SECOND SERIES JANUARY 1942 VOL. 18, NO. 1

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Basic Hemodynamic Principles Essential to Interpretation of Cardiovascular Disorders 3
Carl J. Wiggers

Heart Failure 18
Paul D. White

Arteriosclerosis: Social Significance and Recent Advances in Treatment 36
George Morris Piersol

Recent Studies in the Production of Cancer by Chemical Compounds; the Conditioned Deficiency as a Mechanism 53
C. P. Rhoads

The History of Fever Therapy in the Treatment of Disease 65
William Bierman

Library Notes:

Recent Accessions 76

Proceedings of Academy Meetings 78

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

Published monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York

Entered as second-class matter, February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription, United States, Canada and Cuba, $3.00; all other countries, $4.00 a year. Single copies, 50c.

OFFICERS AND STAFF OF THE ACADEMY

1942

President

MALCOLM GOODRIDGE

Vice-Presidents

I. OGDEN WOODRUFF — ROBERT F. LOEB — HENRY CAVE

Treasurer

RODERICK V. GRACE

Recording Secretary

JAMES RALPH SCOTT

Trustees

GEORGE BAEHR	*RODERICK V. GRACE	WALTER L. NILES
ARTHUR F. CHACE	SHEPARD KRECH	*JAMES RALPH SCOTT
CARL EGGERS	CURRIER MCEWEN	FREDERIC E. SONDERN
*MALCOLM GOODRIDGE	JAMES ALEXANDER MILLER	CHARLES F. TENNEY
	HAROLD R. MIXSELL	

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HERBERT B. WILCOX

Librarian

ARCHIBALD MALLOCH

Consultant to Committee on Library

SAMUEL W. LAMBERT

Executive Secretary
Public Health Relations Committee
E. H. L. CORWIN

Executive Secretary
Committee on Medical Education
MAHLON ASHFORD

Executive Secretary, Committee on Medical Information

IAGO GALDSTON

Library Consultants

LAURA E. SMITH — B. W. WEINBERGER — ARNOLD C. KLEBS

Legal Counsel

FRANK L. POLK, ESQ.

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*

ALFRED E. COHN	ROBERT F. LOEB	PHILIP VAN INGEN
EUGENE F. DUBOIS	ARCHIBALD MALLOCH	KARL VOGEL

MAHLON ASHFORD, *Editor*

---

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JANUARY 1942

BASIC HEMODYNAMIC PRINCIPLES ESSENTIAL TO INTERPRETATION OF CARDIOVASCULAR DISORDERS*

The Ludwig Kast Lecture

CARL J. WIGGERS

Professor of Physiology and Director, Dept. of Physiology
Western Reserve University Medical School

GRAHAM LUSK[1] related that when the founding of the Harvey Society was first proposed, Samuel J. Meltzer expressed grave doubts whether New York physicians could be conditioned to attend scientific lectures. "New York," he said, "is a city devoid of scientific interest. The Academy of Medicine is not a scientific body and has no interest in scientific medicine." The growing popularity of the annual Graduate Fortnight, sponsored by your Academy, certainly attests that this has not been true for some time. Their inauguration was, I understand, due chiefly to the foresight and enthusiasm of Dr. Ludwig Kast, in whose honor and memory these lectures are given. I feel significantly honored by the privilege of delivering such a lecture this evening.

Among the books which I treasure is one purchased at the very beginning of my medical career (1904). It is by Theodore C. Janeway, and its full title reads, "The Clinical Study of Blood Pressure—A Guide

* Delivered October 13, 1941 at the Graduate Fortnight of The New York Academy of Medicine.

to the Sphygmomanometer in Medical, Surgical and Obstetrical Practice, with a Summary of Experimental and Clinical Facts Relating to Blood Pressure in Health and Disease." Janeway reviewed the salient facts of hemodynamics as they were known in that day and upon them built interpretations of blood pressure readings in clinical practice. Only a Janeway could have produced so outstanding a monograph. Its influence in establishing routine blood pressure determinations in the practice of medicine and in our progressive advance in the interpretation of hypo- and hypertension is immeasurable.

During the thirty-seven years that have elapsed, significant contributions of a fundamental nature have been made in our understanding of dynamic aspects of blood pressure and its physiological control. However, a fairly large experience in reading and evaluating publications dealing with the heart and circulation has convinced me that physicians, clinicians, and experimenters, otherwise distinguished, frequently neglect these fundamental principles of hemodynamics in drawing conclusions, while comparatively few utilize the possibilities of interpretation opened by newer discoveries. Consequently I feel that the time has arrived when we should close our eyes and reflect upon the value of what we have seen, done and heard. If my re-analysis of hemodynamic fundamentals seems too elementary to some, or gratuitous to others, I beg their indulgence.

The Pulse Pressure and Pressure Pulse. During each ventricular systole a definite quantity of blood is ejected into the aorta. It is called the *pulse volume*, *stroke volume* or *systolic discharge*. In man, it averages about 62 cc. The interval of ejection is very short; about 0.25 second in man and less in lower animals. Moreover, the output is by no means constant during this period. Fully two-thirds of the total systolic discharge volume is displaced into the aorta in less than 0.1 second and very little is ejected during the last 0.05 second. Since the arteries are already fairly distended with blood at the moment when ejection begins additional room must be made quickly. This is accomplished partly by moving the column of blood onward (kinetic energy of flow), partly by distending the arterial walls and increasing the capacity of the arteries, i.e., it is stored as potential pressure energy.

The pressure changes thus created in the aorta can be recorded accurately in anesthetized animals by inserting a calibrated optical manometer through one of its branches. A typical curve is shown in Figure 1.

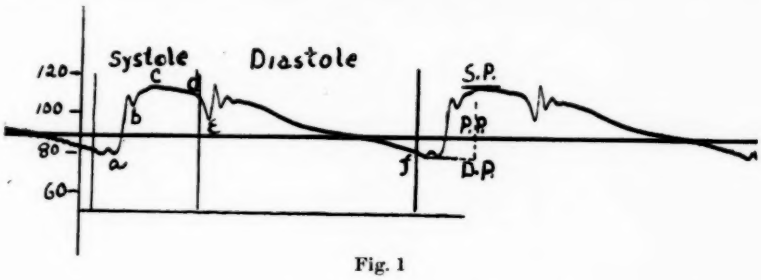

Fig. 1

For about 0.04 second after the onset of ejection (a-b), a great forward movement of blood together with a steep increase in pressure occurs. During the next 0.04 or 0.05 second (b-c), the pressure mounts with a slower gradient to a summit, but the velocity of flow decreases. During the remainder of systole (c-d), both pressure and flow gradually decrease together. The time of closure of the semilunar valves, demarcating the beginning of diastole, is accomanied by a sharp drop in pressure, the incisura (e). The pressure energy available at this moment is the effective force which gradually moves blood stored in the distended arteries through the arterioles into the capillaries during diastole. As conversion of pressure energy to flow occurs, the pressure curve slowly declines during diastole (e, f). Obviously, the conversion of potential energy stored during systole into kinetic energy of flow during diastole insures a reasonably continued flow through the capillaries where the interchange of foodstuffs, salts, water and gases goes on. Such pressure curves reveal also that the pressure in the aortic arch reaches a maximum during midsystole and a minimum at the end of diastole. These are referred to as *systolic* and *diastolic* pressures, respectively, and the numerical difference is called the *pulse pressure.*

The pressure values in mm. Hg *at these moments of the cardiac cycle* are the ones measured by sphygmomanometric methods in man and unanesthetized animals. Obviously, they give no information of the pressure changes between the points. The fact that arterial pressure readings taken by indirect methods only give information regarding pressures at two moments of the cardiac cycle must always be kept in mind in interpretations of clinical blood pressure readings.

The entire course of the pressure changes illustrated in Figure 1 and known as the *pressure pulses* can be ascertained in unanesthetized animals and man by two procedures:

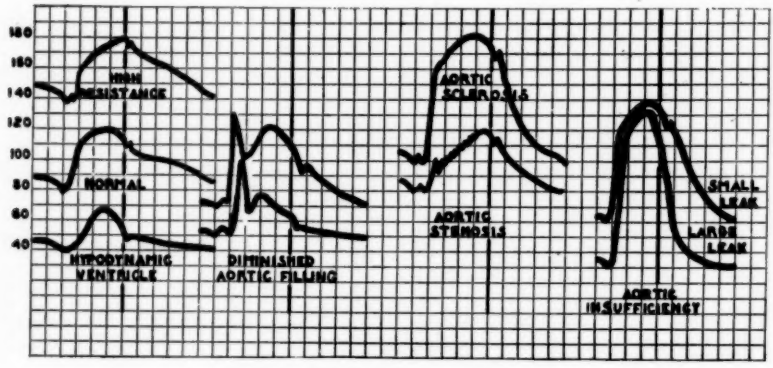

Fig. 2

1. They may be recorded by hypodermic optical manometers of the Hamilton or Gregg patterns. Unfortunately, hypodermic puncture of the subclavian artery is regarded as too hazardous; hence the cubital or radial arteries are more commonly used. Unfortunately, however, the form of the pressure pulse undergoes significant changes by the time it reaches the cubital artery. Their nature and causes cannot be considered tonight (cf. Wiggers[2]). For these reasons, the use of an otherwise admirable method is restricted to particular circumstances under which puncture of the subclavian artery seems warranted.

2. A simpler and harmless procedure, sufficiently accurate for most dynamic studies has been used by the author on patients.[3] A cup is firmly pressed into the supraclavicular fossa of a patient in the sitting posture and a subclavian pulse recorded optically by a Frank segment capsule. Such a record gives the form but not the ordinate values of the pressure pulse. The latter can be supplied by determining systolic, diastolic and brachial pressures in the usual manner and placing them at the crest and trough points indicated in Figure 1. The intervening vertical distance can, if desired, be subdivided proportionally and the pressure value at any moment of the cycle thus established, much as in direct registration of pressures from the aorta in anesthetized animals by optical manometers.

The importance of a knowledge of the contour as well as the maximal and minimal values of pressure pulses in a number of common clinical diseases is illustrated by curves of Figure 2. Lesions of the aortic

valves produce particularly distinguishing features in the central arterial pulses. The pulse of aortic stenosis is characterized by a short sharp rise terminating in an anacrotic V-shaped notch or incisura. The greater the stenosis, the lower this notch. Following this, the pressure rises slowly to a maximum at the very end of systole; in other words, the pressure read as systolic is not that near midsystole as in normal states, but at the end of systole. Moreover, irregular vibrations are superimposed upon the basic form of the curve, thus furnishing a graphic inscription of the systolic murmur.

Analysis of aortic pressure pulses from experimental animals suggests that the central pulse contours in man can probably give information regarding the magnitude of aortic regurgitation. With large aortic valve leakage, the curves rise smartly to a rounded summit and decline appreciably during the latter part of systole. This is the *systolic collapse* which is interrupted by the deep incisura which follows immediately. The latter, continued during the early moments of isometric relaxation, constitutes the *early diastolic* collapse. During the remainder of diastole, pressure declines little, if at all. With smaller leakage of the aortic valves, the contour of the systolic portion is, on the contrary, not significantly altered. The early diastolic collapse is also not great, but the chief drop occurs during the latter portion of diastole. (For further discussion, cf. Wiggers.[2])

During conditions in which the arterial system is not well filled, such as shock, hemorrhage, hyperthermia, the pressure curve rises to a sharp preliminary peak after which a lower and somewhat broader systolic summit is reached. Indeed, the question arises which of these peaks represents systolic pressure. This is of some importance since the differences may be as great as 50 mm. Since the first peak is due to a momentary overshooting in the lax arterial system, the midsystolic peak is the more reasonable index of systolic pressure, but auscultatory sphygmomanometer readings probably correspond to the former. The practical import of such discrepancies is that the systolic pressure of patients after hemorrhage or during shock appears higher than it actually is, therefore giving the false impression of a favorable prognosis. I have a suspicion that many clinical reports that systolic pressure can be high when a patient is in a serious state are due to too complete reliance on auscultatory readings, and an insufficient regard to the fact that the midsystolic pressure may be much lower, as shown in pressure pulses.

Factors affecting systolic and diastolic pressure. Since arterial pressures are determined by the degree to which the arterial walls are distended and placed under tension, *any factor that increases the volume of blood in the arterial tree increases pressures; and, vice versa, any influence that diminishes the arterial volume, reduces pressures.* This is so fundamental that it might be called the first law of hemodynamics. The primary variables affecting such arterial distension are the systolic discharge, the heart rate, and the peripheral resistance which is determined chiefly, but not wholly, by arteriolar constriction. However, increase in these three variables does not elevate systolic and diastolic pressures equally. Measurements of systolic and diastolic pressures, therefore, become most significant when their relative changes or the pulse pressure are evaluated. The effect of each influence acting separately has been predicted by mathematical considerations and theoretical analyses, taking into account the volume elasticity curves of the normal aorta. Thus, if the distensibility of the aorta be expressed as $^{dp}/_{dv}$ and the volume of the aorta as V, then as long as $^{dp}/_{dv}$. V remains constant, the pulse pressure (dp) increases or decreases when either the systolic discharge (dv) or the capacity of the aorta (V) alters. When $^{dp}/_{dv}$. V is not constant, changes in pulse pressure are not easily predictable, but must be determined experimentally, with the aid of artificial models or animals. There is another reason why experimental studies are required to check mathematical predictions. The latter are generally based on the assumption that the volume of the aorta changes instantly at the beginning of systole and after closure of the semilunar valves. This does not occur in the body, as we have seen. However, on the whole, the results of experiments can be harmonized with theoretical considerations.

It can be shown by use of artificial circulation machines of proper design (cf. Wiggers[2,3]): *1*, that increasing the systolic discharge elevates systolic pressure more than diastolic, the pulse pressure being greater; *2*, that acceleration of the heart raises diastolic pressure more than systolic, the pulse pressure being smaller; and *3*, that augmenting the peripheral arteriolar resistance elevates diastolic pressure more than systolic, the pulse pressure decreasing.

The last of these dynamic postulates is apparently in conflict with the bulk of clinical observations on hypertension. As is well established, hypertension is also due predominately to an increase in peripheral resistance but almost invariably systolic pressure is increased more than

diastolic and the pulse pressure is larger. Even in so-called "high diastolic types" of hypertension the pulse pressure is never smaller than normal. In other words, hypertension is not wholly defined in a dynamic sense as an elevation of blood pressures, but as a disproportionately greater rise of systolic compared to diastolic pressure. As shown in Figure 2, the contour of the pressure fluctuations also deviates from the normal; the pressure rises abruptly during systole to a high level and the diastolic limb shows a rapid decline. Indeed, these features may be so pronounced that the pressure pulses somewhat resemble those of aortic insufficiency; the differences, of course, being that diastolic pressure is elevated in the former and depressed in the latter (Fig. 2).

The paradox that in dynamic models of the circulation an increase in peripheral resistance reduces pulse pressure, whereas in clinical and experimental hypertension a similar increase in resistance augments the pulse pressure has interested me for a number of years[4,5] and led to considerable experimental work as well as recordings on patients in efforts to clarify the situation.

Evidence summarized elsewhere[5] led to the conclusion that the larger pulse pressure in hypertension can only be explained by a concurrent decrease in the elasticity of the aorta. This fits with studies on a physical circulation model, for if, in addition to an increase in peripheral resistance, the aortic elasticity is reduced, systolic pressure rises still more while diastolic pressure decreases. This means, for example, that aortic sclerosis is unfavorable in increasing systolic, but favorable in reducing diastolic pressure. The pulse pressure obviously increases greatly and a condition of so-called "systolic hypertension" is created. Two important corollaries follow: *1*, Aortic sclerosis or any other factor which reduces aortic distensibility accentuates the elevation of systolic pressure but tends to reduce diastolic pressure. *2*, An essentially normal diastolic pressure in hypertension is not necessarily a favorable sign which indicates that peripheral resistance is normal. More often it denotes extension of a process to the larger arteries and particularly the aorta.

Nature seems to have provided a mechanism by which the dynamic effects of diminishing aortic distensibility, such as occur with advancing age, is at least partly compensated by an increase in the size or capacity of the aorta. Such an increase in size has the same effect on systolic and diastolic pressures as a decrease in systolic discharge would have with the diastolic size of the aorta unchanged. Either, if superimposed on a

primary vasoconstriction, tends to reduce the systolic pressure more than the diastolic.

There would seem to be no question but that arteriosclerotic changes discovered in the aorta at autopsy contribute to the high systolic pressures and account for the large pulse pressure in some cases of hypertension. But the aortic changes need not necessarily be due to visible morphological changes; they may not even be detectable in comparative determinations of volume elasticity coefficients of aortic cylinders or rings obtained at autopsy. On the contrary, there is increasing experimental evidence that aortic elasticity and capacity can change functionally. On the basis of studies on pulse velocities in central vessels, Böger and Wezler[6] believed they had shown that aortic elasticity is greatly reduced, particularly in the so-called "red hypertension" of German clinicians. Personally, I have not been convinced that changes in pulse velocity are sufficiently accurate to allow such deductions.[4, 5] But in experiments on normal dogs, Wégria and I[7] were able to show that in acute hypertension initiated primarily by nervous and hormonal actions on peripheral arterioles, the initial passive expansion of the aorta is followed by an active diminution in size and, after a further latency, its elasticity is *increased*. In such experiments the effects of decreased size of the aorta overbalanced the opposing effects of an increased elasticity in raising systolic pressure. While we have no reason to conclude that these or similar conditions necessarily occur in clinical or experimental hypertension, they do stress the importance of functional changes in aortic capacity and elasticity as factors which determine the height to which systolic pressure rises.

To summarize, clinical and experimental hypertension is initiated by an increase in peripheral arteriolar resistance, but intensified as far as systolic pressure is concerned by functional or morphological changes in aortic capacity and/or elasticity. The cardiac output is only rarely increased, e.g., in cases of hypervolemia and thyrotoxicosis.

This aspect of hypertension complicates the interpretation of therapeutic claims made for agents which reduce blood pressure. The mere demonstration that a substance is capable of lowering systolic pressure is not tantamount to proof that this has been accomplished through abolition of the arteriolar constriction which initiated the high pressure. It has long been obvious that the high arterial pressure of hypertension can be reduced by drugs which cause an extreme slowing or depression

of the heart, a procedure which must be condemned as harmful as far as maintenance of a circulatory balance and adequate blood flow through tissues is concerned. That pressure reducing agents may also act on the aorta must at least be considered a possibility in view of newer evidence. If, by any chance, they should act by causing an extreme dilatation of the aorta, the value of such reduction of hypertension might be highly questionable. In short, it is not sufficient to establish therapeutically that drugs and various preparations reduce hypertension; it is even more important to know how they act. This would appear to be the next important step in the field of experimental work on hypertension.

Mean pressure. In experimental work, the lateral mean pressure in the aorta is commonly recorded by measuring the end-pressure in one of its accessible branches (e.g., carotid or femoral artery). This must be done by a properly damped Hg manometer, i.e., one in which the cardiac oscillations are barely discernible. Registration of wide fluctuations, as is still too common a practice among experimenters, renders readings of mean pressure inexact. The low period of Hg manometers prevents their recording either the systolic or diastolic pressure with exactness. The magnitude of error varies extremely under different conditions and the error may be opposite in direction at various times. For example, at very slow heart rates the momentum of the mercury column causes it to overshoot both during its ascent and descent, with the result that systolic pressure is recorded too high and diastolic pressure too low; on the contrary, at very rapid heart rates, the inertia of the mercury prevents full systolic and diastolic pressure from being reached, with the consequence that systolic pressures are recorded too low and diastolic pressures too high. All of these facts have been well-known since the introduction of the recording mercury manometer by Ludwig; but they seem to have escaped many experimenters who continue to speak of systolic pressure and pulse pressure thus recorded; hence this reiteration.

The mean pressure represents the average pressure during a succession of cardiac cycles and gives less explicit information than systolic and diastolic pressures. Owing to the form of the pressure pulse, it is never a mathematical average of systolic and diastolic pressures. As a matter of fact, a mean pressure is non-existent; but is a convenient fictitious value which has proved useful in hemodynamic considerations. Thus, it is commonly stated that as long as minute output of the heart

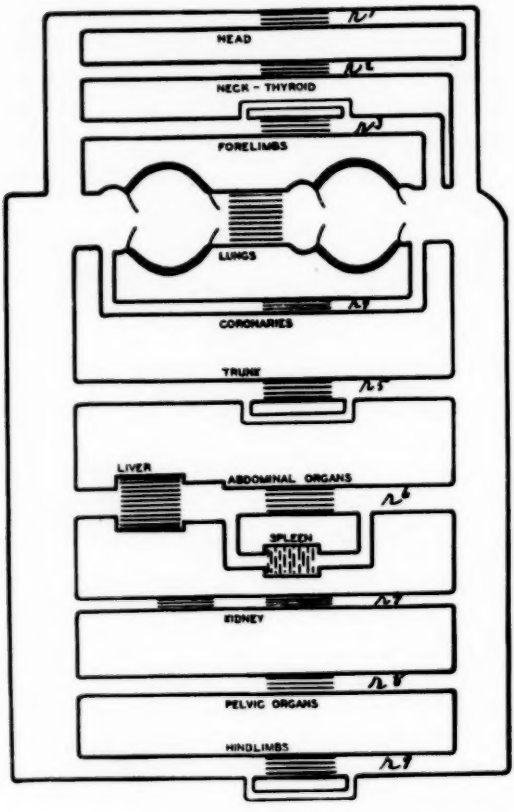

Fig. 3

does not change, any elevation of mean pressure denotes an increase, and a fall of mean pressure, a decrease in total resistance to runoff from the aorta, for changes in aortic elasticity do not affect the mean pressure. This resistance is due chiefly to friction in the various arterioles, capillaries and venules and to the additional resistance offered by venous pressures and viscosity of blood. As all students of hemodynamics are aware, the total peripheral resistance cannot be treated by regarding the circulation as having one resistance only. As shown in Fig. 3, it is composed rather of a series of parallel resistances, and, as in similar parallel resistances of an electric circuit, the *total resistance* is calculated as

$$1/R = 1/r^1 + 1/r^2 + 1/r^3 + 1/r^4 \text{----------} 1/r n.$$

A calculation of such a total resistance can be made in absolute units or it can be expressed as arbitrary units provided we know the mean pressure and rate of runoff, e.g., resistance $= \frac{\text{pressure}}{\text{rate of flow}}$. Since all of the blood ejected from the left ventricle during systole must leave the arterial system when mean pressure has reached an equilibrium, we can use cardiac output per minute or per second in such equations, as an index of rate of flow.

In this way, Frank, Böger and Wezler and others have used the formula

$$R = \frac{Pm \times 1332}{Vt} = \frac{\text{dynes. sec.}}{\text{cm.}^5} \text{ (absolute units).}$$

Pm denotes mean pressure in mm. Hg, 1332 represents a conversion factor to absolute units, and Vt represents the output per second. Resistances so measured range from 539 to 1150 absolute units in man, 2060–9080 A.U. in dogs and from 11,620 to 12,590 A.U. in rabbits. In other words, as might be expected with approximately equal mean pressures, the actual resistance varies inversely with the size of the animal, e.g., it is 11-13 times as great in rabbits as in man. For this reason, Bazett and associates[8] found it advisable to introduce a factor for body size or surface area and suggested the arbitrary formula $R = 3\frac{PM}{Vt/A}$, in which A represents surface area, and Vt/A, the cardiac output index of Grollman. The factor "3" was arbitrarily introduced so that normal values in man would conveniently range around 100 (variations 79-138).

The use of such calculations may however contain a trap; if so, I have unwittingly fallen into it with other investigators in calculating peripheral resistance in patients with hypertension.[4] Preliminary experiments on dogs reported in association with Dingle, Kent and Williams[9] showed that when mean arterial pressure was increased to equal levels by reflex action, adrenalin, pituitrin, mechanical clamping of vessels, etc., the absolute resistances calculated from simultaneous records of cardiac output (oncometer) and mean pressure did not show the correspondence anticipated. Since Wégria and I had shown that such a rise in pressure is accompanied by a decrease in the capacity of the aorta, we suggested that this may be a factor which vitiates such calculations of total resistance.

If the magnitude of change in total peripheral resistance cannot be

evaluated quantitatively by such methods, there is still less chance that it can be inferred from variations in mean pressure, as is frequently done. Such inferences contain several sources of error. In the first place, any tyro in hemodynamics realizes that mean pressure cannot be used as an index of vasomotor power or peripheral resistance when the output of the heart changes simultaneously. However, the possibility of such changes in cardiac output are too often ignored, or it is assumed that they do not exist. The latter is a fallacy, for extensive observations on cardiac output by cardiometric registration has convinced me that pressor nerves or drugs which have no direct action on the heart generally do alter venous return and, secondarily, the cardiac output, in accordance with Starling's law. The sad fact remains that despite such knowledge, our best journals abound in reports, dealing with hypertension, shock and hemorrhage, localization and vitality of vasomotor centers, assay of drugs and hormones, etc., in which changes in mean pressure are used as a quantitative index of vasomotor power without controls of cardiac output.

However, assuming that reasonable proof is obtainable that changes in cardiac output are not significant, a second problem arises: Does the absolute or percentile change in mean pressure offer the better quantitative criterion of vasomotor power? In analyzing the observations that stimulation of pressor nerves generally causes less rise of pressure when the initial pressure is low than it does when it is normal, Porter[10] in 1907 offered the following analogy: "An unfaithful trustee robs two women. One of these has $40,000, the other $20,000; from each he took $10,000. Their absolute loss is the same, but one woman can still live on her income, while the other must work or beg." To this, Sollmann and Pilcher[11] retorted, "With the same absolute loss, the percentile loss of the two women is different, it is true; but the percentile gain of the trustee is the same in both cases. *A priori*, it is not clear whether the blood pressure is playing the role of the trustee or of the women." The questions thus started have never been settled. Our own efforts to do so failed when no consistent changes in calculated absolute resistances could be obtained. It remains for some genius in circulatory dynamics to find a way out of the present impasse. Attempts at statistical treatment, such as have been made, are, of course, no better than the value of the original data utilized. Finally, no one has even suggested a hemodynamic basis upon which absolute or percentile changes in *systolic*

pressure could serve as an index of vasomotor power. Nevertheless, even such studies have been made to test the relative potency of carotid sinus reflexes on the vascular system in normal and hypertensive subjects.

Investigators have, it is true, attempted to verify the existence of vasomotor changes by studying blood flow or volume changes in separate organs. The use of plethysmographs and oncometers constitutes a considerable advance when changes in a particular organ are concerned. Thus, when the mean pressure and volume of an organ alter in opposite directions, it usually denotes vasomotor change *in that organ*. Caution must, however, be observed in *extending* such interpretations. Changes in volume opposite in direction to blood pressure certainly do not mean that cardiac output is not concerned in the mean blood pressure changes obtained. This is obvious after injection of epinephrine, which generally causes an elevation of pressure and reduction in kidney size. The sampling of vasomotor reactions or vascular resistance in individual organs or the limbs—a common practice in studies on hypertension—is also not a safe index of the total resistance to aortic runoff from all of its branches. This is obvious from the formula in calculation of R. If r^1 or r^3 increases, a corresponding change in the opposite direction in r^2 or r^4 would leave R unaffected. Thus the demonstration that the rate of blood flow in the hands or arms is no greater than in hypertensive subjects does not prove that the high blood pressure is due to generalized constriction.

Demonstrated constriction in organs supplied by the mesenteric vessels can with more reason be accepted as leading to increased total resistance because the "splanchnic area" is dominant in affecting total peripheral resistance. It is possible, for example, to ligate all branches of the aortic arch—except the carotid arteries which start distorting sinus reflexes—as well as the descending aorta below the inferior mesenteric branch without causing elevation of aortic mean pressure or changes in calculated peripheral resistance. However, ligation of the superior mesenteric vessel, in addition, definitely increases both.

Résumé. Results of investigations on the circulation would be more concordant and the literature on the subject less confused if investigators and clinicians in general restricted their deductions and conclusions to those that are allowable on the basis of established fundamentals. The following principles were discussed:

1. The pressure variations created in the aorta by each discharge of

the left ventricle not only have a magnitude which is defined by readings of systolic and diastolic pressures, but a definite form which is manifested in optical records of the central arterial pulse. Significant changes in contour of importance in clinical conditions are graphically pictured in Figure 2, and briefly discussed.

2. Measurements of systolic and diastolic pressures only yield full information when their relative deviations, i.e., changes in pulse pressure, are considered. Dynamically, systolic pressure increases more than diastolic (pulse pressure larger) when the systolic discharge of the heart increases and when the capacity of distensibility of the aorta decreases. Diastolic pressure increases more than systolic (pulse pressure less), due to cardiac acceleration and increase in total peripheral resistance. Since a number of these reactions generally occur together in the body, their value in interpreting blood pressure changes has not proved as great as was at one time hoped.

3. Hypertension is not defined dynamically as an increase in blood pressure alone; the pulse pressure is always increased to varying degrees. This greater pulse pressure is generally due to decreased distensibility of the aorta and not to the increased peripheral resistance. There is reason to suspect that hypertension with little or no elevation of diastolic pressure is associated with a significant decrease in aortic elasticity.

4. Before agents which reduce blood pressure in clinical or experimental hypertension are acceptable therapeutically, it must be shown that they in fact reduce total peripheral resistance and that depressor reactions are not due to action on the heart or aorta.

5. Mean pressure is a fictional value which represents the mean of successive pressure changes in the aorta. It can fortunately be recorded directly by a highly damped mercury manometer. Writers should avoid erroneous statements or inferences that changes in pulse pressure can be gauged by such recordings.

6. The reciprocal of the total resistance is given mathematically by the sum of the reciprocals of resistances in parallel circuits of the arterial system. The resistance, calculated by the ratio $\frac{\text{mean pressure}}{\text{cardiac output}}$ increases progressively with body size, but the validity of such estimates is often reduced by the fact that possible changes in aortic capacity are not taken into account.

7. Elevations of mean arterial pressure can be attributed to changes

in total peripheral resistance only when it is proved simultaneously that the minute output of the heart or the capacity of the aorta has not changed actively. Since this does not happen under any circumstances known to the writer, changes in mean pressure, either absolute or percentile, cannot be used as a quantitative index of the intensity of arteriolar constriction or of the degree of activity of the vasomotor center.

8. The sampling of vasomotor reactions or vascular resistance in individual organs or limbs—a common practice in studies on hypertension—does not allow the conclusion that total peripheral resistance is increased or that such increase is the chief cause of the hypertension.

9. Finally, the themes are stressed that experimental results are no better than the apparatus employed, that the analysis of dubious results cannot be improved by statistical methods, and that the breadth of conclusions drawn should not exceed the limitations permitted by the most accurate results.

REFERENCES

1. Lusk, G. The Harvey Society, *Harvey Lectures*, 1929-30, *25:*205.
2. Wiggers, C. J. *Physiology in health and diseases.* 3. ed. Philadelphia, Lea & Febiger, 1939, pp. 615; 723.
3. Wiggers, C. J. Influence of vascular factors on mean pressure, pulse pressure and phasic peripheral flow, *Am. J. Physiol.*, 1938, *123:*644.
4. Wiggers, C. J. Dynamics of hypertension, *Am. Heart J.*, 1939, *16:*515.
5. Wiggers, C. J. Physical and physiological aspects of arteriosclerosis and hypertension, *Ann. Int. Med.*, 1932-33, *6:*12.
6. Böger, A. and Wezler, K. Die Bestimmung des arteriellen Gesamtwiderstandes am Menschen, *Arch. f. exper. Path. u. Pharmakol.*, 1937, *186:*43; and Die Einteilung der verschiedener Hochdruckformen nach kreislaufmechanischen Gesichtspunkten, *Klin. Wchnschr.*, 1939, *18:*401.
7. Wiggers, C. J. and Wégria, R. Active changes in size and distensibility of the aorta during acute hypertension, *Am. J. Physiol.*, 1938, *124:*603.
8. Bazett, H. C., Cotton, F. S., Laplace, L. B. and Scott, J. C. Calculation of cardiac output and effective peripheral resistance from blood pressure measurements, *Am. J. Physiol.*, 1935, *113:*312.
9. Dingle, J. T., Kent, G. T., Williams, L. L. and Wiggers, C. J. Study of alleged quantitative criteria of vasomotor action, *Am. J. Physiol.*, 1940, *130:*63.
10. Porter, W. T. and Marks, H. K. Effect of hemorrhage upon the vasomotor reflexes, *Am. J. Physiol.*, 1908, *21:*460.
11. Sollmann, T. and Pilcher, J. D. Reactions of the vasomotor centre to sciatic stimulation and to curare, *Am. J. Physiol.*, 1910, *26:*233.

HEART FAILURE*

The Wesley M. Carpenter Lecture

PAUL D. WHITE

Physician, Massachusetts General Hospital
Lecturer in Medicine, Harvard Medical School

"A CERTAIN man became very breathless and grew thin. All observers blamed the lungs. When the cadaver was opened nothing remarkable was found in the lungs, but the heart, mirabile dictu, equalled the size of a large head; it was so large that it contained all the blood and spirit." This case cited by Ballonius and published by Theophilus Bonetus in the first edition of the *Sepulchretum* in 1679 was, so far as I know, the earliest instance recorded of the association of enlargement of the heart, that is, of heart disease, with dyspnea doubtless due to heart failure.

"A very fat poet who for a long time had suffered from asthma and frequency of urination and for some little time also from dull pain in the left side, spent a convivial evening at dinner with friends and relatives reciting to them all manner of odes, both hilarious and sad, including even a funeral lamentation. At nine o'clock he rose from his seat and as he made the effort of mounting the stairs he was seized with an increasing difficulty in drawing his breath. Aided by his secretary, with great effort he reached his couch, reclined, accepted absolution, and expired. The next day when his abdomen was opened, everything was found loaded with fat. His abdominal wall measured three fingers in thickness and his omentum easily weighed 30 civil pounds. The liver and spleen were large, the bladder small and weak. The heart was rather large and the coronary blood vessels were unexpectedly and extensively bony with thin membranes covering the bone on both sides, and in two places the bony walls were so completely contiguous that not even the point of a fine needle could enter. The lungs were large."

This case cited by Bonetus himself and published in the second edition of the *Sepulchretum* in 1700 was, to the best of my knowledge, the first recorded instance of the association of rapid death with a high de-

* Presented at the Graduate Fortnight of The New York Academy of Medicine, October 13, 1941.

gree of coronary disease, quite probably a fatality from coronary occlusion. It antedates Heberden, Jenner, and Parry by nearly a hundred years, and although casually referred to by Morgagni in 1761, has apparently escaped the notice of the generations that have followed.

The fact that the recognition of these serious end results of heart disease came so slowly, and not until the Seventeenth and Eighteenth centuries, is of course to be ascribed to the rarity of autopsies in earlier days, to the cursory examination of the viscera in those that were done, and to neglect of good history taking. But to think that the essence of knowledge about these things is new in our own generation is an error and unfair to those who have gone before us. "Men were not all cowards before Agamemnon or all fools before the days of Virchow and Billroth." Because of the general ignorance about the valuable cardiovascular contributions of some of the medical leaders of their day, two or three centuries ago, and because these contributions sum up the essence of our present day knowledge of the mechanism and symptomatology of the congestive phenomena of heart disease, I shall take a few minutes to give you some pertinent quotations.

Even before the *Sepulchretum* of Bonetus, Richard Lower, who was the first to transfuse blood by tubes from one animal to another, wrote in 1669 of experimental compression of arteries and veins with the resultant congestion; he also described constriction of the heart in man by pericardial effusion and by a thick and hard pericardium.

In 1715 Vieussens described very well a case of mitral stenosis. He added the following observation. "The opening of the auricle into the ventricle was so stenosed that the blood could no longer freely enter. The circulation was, therefore, so embarrassed that it began to cause an extraordinary dilatation of the pulmonary veins and retarded the passage of blood through all the vessels of the lungs, which became so engorged that they compressed the air vesicles and hindered the free entrance and exit of air to and from them; which explains why the patient always breathed with difficulty."

Vieussens also wrote of acute and chronic pericardial constriction of the heart, diagnosing correctly one of the acute cases. Incidentally he described the waterhammer or Corrigan pulse in a patient with aortic regurgitation.

But it was Lancisi, remarkable physician to Pope Clement XI in Rome, who deserves the most credit for analyzing the sequence of events

leading to heart failure. On page 136 of his book, *De Motu Cordis et Aneurysmatibus,* published posthumously in 1728, it is stated that obstruction to the course of blood either in the heart or in the major vessels is obviously a cause of enlargement of heart and blood vessels, most readily of the auricles and veins because of their thin walls. He cited on the next page the case of a clergyman of St. Peter's at the Vatican who was troubled by suffocative asthma and vertigo and who showed at autopsy calcareous aortic stenosis and cardiac enlargement. He added the significant statement that the strenuosity of this clergyman's body and mind was such as to cause an increased blood flow with so rapid a return of blood to the heart that heart chambers, lungs, and veins were overfilled, ample reason, he said, for the dyspnea and enlargement of the right heart chambers. Thus Lancisi presented an exciting or secondary factor, as well as an organic or primary one. Furthermore on page 141 Lancisi added the following remarks: "From dilatation of the right auricle and ventricle two results develop which cause dilatation of the jugular veins and are worthy of the greatest consideration. The first of these is the overfilling of the right heart chambers and hence the jugulars with blood. The second is the insufficiency of the tricuspid valve due to the dilatation of the right heart chambers, which insufficiency allows the transmission of the pulsation of the ventricle backward into the right auricle and venae cavae as well as forward into the pulmonary artery." This he called a new sign ignored by earlier authors, partly because it was not noted post mortem.

Senac and Morgagni followed suit, the former in 1749, the latter in 1761. Senac emphasized, as Lancisi had not done, that even the stout, thick-walled left ventricle might be dilated and enlarged, as he found it to be in a case of aortic stenosis. "If the left ventricle," said he, "must dilate when it cannot empty itself, the dilatation then must involve even more its auricle and the pulmonary veins." Of Lancisi's case he wrote: "The blood was arrested in the lung, hence the asthma and the dilatation of the right ventricle, its auricle and the vena cava." He also wrote of the finding of edema of the feet in some cardiac cases, and of hydrothorax.

Morgagni spoke of the slow course of the heart failure in some cases and he too described the sequence of events in a young man with aortic regurgitation. "You will perhaps ask," he said, "why, as all the four cavities of the heart were dilated in the young man in question the dila-

tation of the left ventricle was, nevertheless, the greatest? Without doubt, because the dilatation of the ventricle had given rise to the dilatation of the other ventricle and the two auricles; that is, by admitting a less quantity of blood than it ought, for the reason which I just now gave you; and, in consequence of this obstruction, by retarding the motion of the blood in the left auricle, in the lungs, in the right ventricle, and its adjoining auricle. But why was the left ventricle the first of all to be dilated? Why, certainly, because the semilunar valves, whatever the cause of this circumstance might be, having been contracted and corrugated, could not properly expand themselves, so as to prevent the blood from being, in part, sent back into the ventricle, from whence it came."

One more historical reference to wind up the important but much neglected statement of the debt we owe our forbears for ideas about heart failure. Hope's writings are much better known and date back to only a little over a hundred years ago (1832) but they are so clear and additionally helpful that they are worth quoting in brief. "As an obstacle to the circulation operates on the heart in a retrograde direction, the cavity situated immediately behind it is the first to suffer from its influence. Accordingly all the impediments seated in the aorta, its mouth, or the arterial system, act primarily on the left ventricle, which being likewise exposed to the heaviest burden when the circulation is accelerated, has to conflict against a greater variety of exciting causes of hypertrophy, than any other cavity of the heart. . . .

"So long as the left ventricle is capable of propelling its contents, the corresponding auricle, being protected by its valve, remains secure. Hence, in a large majority of cases, the auricle is perfectly exempt from disease, while the ventricle is even enormously thickened and dilated. But when the distending pressure of the blood preponderates over the power of the ventricle, its contents, from not being duly expelled, constitute an obstacle to the transmission of the auricular blood. Hence the auricle becomes overdistended and the obstruction may be propagated backwards through the lungs to the right side of the heart, and there occasion the same series of phenomena. . . .

"When the mitral orifice is contracted, especially if the aperture be very small, . . . the left auricle, having to struggle against the contracted valve in front, and also to sustain the distending pressure of the blood flowing in from the lungs, invariably becomes thickened and di-

lated. The engorgement, extending backwards through the lungs to the right ventricle, occasions its hypertrophy and dilatation; under which circumstances, namely, hypertrophy of the right ventricle and contraction of the mitral valve, the lungs suffer in a preëminent degree (as said Vieussens a hundred years earlier); for, being exposed to the augmented impulsive power of the right ventricle behind, and incapable of unloading themselves on account of the straitened orifice in front, their delicate and ill-supported vessels are strained beyond the power of resistance. . . .

"When the impediment to the circulation is primitively seated in the lungs, the right ventricle, situated immediately behind them, is the first to experience its influence. . . .

"The primary effect of universal obstruction of the lungs by engorgement, is, to produce oedema of their cellular tissue and dyspnoea; whether the latter depends solely on the engorgement or *partly also on spasm of the bronchi excited by the irritation of that congestion* (italics, mine), is difficult positively to determine, though the latter is highly probable. . . . The secondary effect is, to gorge the right side of the heart, and thus impede the return of the venous blood from the system at large; which cooperates with the increased energy of the arterial circulation in producing anasarca."

Why was it that these evidences of heart strain and heart failure were discovered so near the beginning of any knowledge of heart disease, two centuries or more ago? Because they are of course such gross and often terminal conditions that they naturally could not help but excite speculation before death and interest in the findings post mortem. There was nothing delicate or mysterious about the situation except in some of the details which have been so well elucidated by many authorities in a resurgence of interest in heart failure in our own generation. I do, however, even while recognizing the need of ample knowledge of this very subject, protest against such an observation as that made by Lewis on page 1 of both editions of his book on heart disease, namely, "The very essence of cardiovascular practice is recognition of early heart failure and discrimination between different grades of failure." I admit that it is necessary to diagnose and to treat heart failure when it comes, but I am sure that we should regard this task as of minor importance compared to both the search for the presence of heart disease before failure comes, and the recognition of the fundamental causes

of heart disease even before the heart has become affected or at least seriously involved. To be sure we can't always do much to combat these factors as yet or to prevent or delay heart failure, but often we can do something, and in that direction obviously lies the hope of the future. I dare say we shall always have victims of heart failure among us, but if such failure can be limited or postponed to old age we may feel that we have accomplished much. Of greater importance than the diagnosis and treatment of heart failure are studies of the causes of heart disease and of its presence before the heart fails.

Before proceeding further it is wise for me to define a little what we mean by "heart failure" as a term in common use and as already illustrated by the historical quotations I have given you. When death comes, the heart stops beating, no matter what disease is fundamentally the cause of the death. But that is not what we mean by heart failure unless heart disease is the essential cause. The heart may suffer from the toxicity of infection or from disease of other organs such as kidneys or thyroid gland, but only rarely to the degree of being responsible for failure; rheumatic fever and diphtheria are among the rare exceptions to that statement. Nor do we label as heart failure the results of hemorrhage or traumatic or vascular shock when, from decrease of circulating blood or vasomotor paresis, the heart receives too little blood to keep up the vital circulation to brain and elsewhere. This is circulatory but not heart failure, though the one on occasion may excite the other.

Nor do we ordinarily label as heart failure conditions in which the fault lies in the inability of the heart to maintain an adequate supply of blood to the arteries, capillaries, and tissues of the body because of some abnormality of the heart structure itself or of its mechanism while the myocardium remains strong. To be sure such trouble is due to failure of the heart itself to "deliver the goods" and might well be called a type of heart failure. In fact it has sometimes been labelled "forward heart failure" in contrast to congestive heart failure, and it is perfectly reasonable to regard it as such. Incidentally the causative factors may lead to congestive failure in its turn.

Those factors which cut down the output of blood into the arterial system, either with or without congestive phenomena essential to them, are as follows. First, those that need not be attended by congestion are aortic stenosis, excessive heart rates in paroxysmal tachycardia, and high

grade sinoauricular or auriculoventricular heart block, conditions that may lead to syncope and even to death, as when aortic stenosis sufficiently cuts down the coronary circulation in middle age or later, when ventricular tachycardia fades into ventricular fibrillation, or when ventricular standstill lasts more than a few seconds. Second are those obstructive states that are attended by both limited output of blood and congestive phenomena, without necessarily any muscle weakness or failure, namely, mitral stenosis, tricuspid stenosis, and constrictive pericarditis, acute and chronic; in these conditions the congestive phenomena are generally much more prominent than the effects of a limited blood supply to the arteries and arterioles and it is, therefore, this very group that is often mistaken for congestive heart muscle failure. Third is myocardial failure itself which is also attended preponderantly by congestive phenomena.

Finally, there is still one more set of cardiac abnormalities responsible for inability or failure of the heart to maintain an effective circulation, namely, various congenital defects. One of the most striking of these is the large auricular septal opening which causes the right heart chambers and pulmonary circulation to be overloaded with blood and hence congested without myocardial failure. Another anomaly acts just reversely to deprive the pulmonary circulation of blood and to overload the aorta and systemic circulation with poorly aerated blood, namely, the tetralogy of Fallot with its pulmonary stenosis, ventricular septal defect, and dextroposition of the aorta. A patent ductus arteriosus puts a burden of variable degree on both sides of the heart but this is usually not great and rarely leads to heart failure per se. Some of the extreme congenital anomalies result in death in early infancy due to the impossibility of the maintenance of an adequate circulation to the body as a whole and not necessarily to heart failure itself.

Having thus presented a large group of conditions in which the heart is structurally or functionally unsuccessful in maintaining a proper circulation, but in most of which the myocardium itself is clinically sound, we come to the two major types of heart failure as they are popularly known, namely, myocardial or congestive failure, and coronary insufficiency or coronary failure. The latter is fundamentally a vascular disease but since the coronary arteries are practically a part of the heart's structure, their serious involvement with resulting inadequate blood supply to the heart muscle, can justifiably be accounted a type of heart disease and of heart

failure, called by Lewis and others the anginal type in contrast to the congestive type. Let us consider this coronary species of heart failure first, leaving for the end the kind that is more commonly thought of by the medical profession when heart failure is mentioned. Failure of the myocardium to receive an adequate blood supply is as a rule first shown by the symptom of angina pectoris and by characteristic electrocardiographic changes on effort. If the coronary circulation is blocked by a thrombus, then the pain (the status anginosus) lasts for hours, until the affected bit of heart muscle dies, while the electrocardiographic changes develop more extensively and last for days or weeks or even permanently. Recovery may be complete or death may come suddenly, even in the very first attack of angina pectoris, due probably to the development of ventricular fibrillation. Such a death is sometimes a just basis for the term sudden death from heart failure. Or, anginal failure may evolve after myocardial infarction or when superimposed on another kind of heart disease, hypertensive, for example, into considerable cardiac enlargement and congestive failure. But heart failure of the coronary type is evidenced only by angina pectoris or characteristic electrocardiographic abnormalities, and not by its various complications, including even death itself which cannot be called coronary with certainty without the presence of one or the other manifestation just mentioned. It is reasonable, however, to assume that a person who dies suddenly after recurrent attacks of angina pectoris has died a "coronary heart failure" death.

Now let us turn to congestive heart muscle failure about which the early authorities wrote and which is what we mean in the great majority of cases when we use the unqualified expression "heart failure." I want to emphasize a few important points about the causes, manifestations, diagnosis, and treatment of heart failure based largely on my clinical experience of the last two decades. Myocardial failure may be quite rapid in its development but it is usually slow and often insidious, though discernible if adequately sought for in an early and slight stage; it is never instantaneous as is the case with heart failure of the anginal type. It is always preceded by obvious cardiac enlargement; hence when dyspnea and edema are found with a heart of normal size they cannot be ascribed to heart muscle failure but must be credited to other causes of congestion. Heart muscle failure may begin on the left side or on the right side, or, least commonly on both sides of the heart simultaneously.

The factors responsible for heart muscle failure are almost as numerous as the causes of heart disease itself. They are best divided into primary and secondary factors. Sometimes multiple factors are responsible in a given case. Rarely the cause is unknown or undiscoverable.

Drs. Boyer, Leach, and I analyzed two years ago the primary and secondary factors responsible for congestive heart failure in 1000 cases, 500 from the wards of the Massachusetts General Hospital and 500 seen in private practice. Our experience will naturally differ somewhat from that of others who live where rheumatic fever is less common and syphilis or anemia more common, or who are pediatricians with the rheumatic group making up almost the total percentage. Actually we found that in our group hypertension as an underlying strain, with or without coronary heart disease, topped the list with a total of 47 per cent, rheumatic heart disease was second with 26 per cent, and uncomplicated coronary heart disease, that is, uncomplicated except by myocardial infarction, was third with 16 per cent. No other factor was responsible for as much as 5 per cent. Lues, for example, accounted for but 3 per cent, the cor pulmonale for 2 and congenital defects for only 1. Four per cent were of unknown origin. Males outnumbered females about two to one in the entire group of 1,000 cases.

Of even more interest were our findings with respect to precipitating factors superimposed on the underlying causes to set off the failure. Auricular fibrillation led the list of the recognizable complications, being clearly responsible for 14 per cent, doubtless due to the associated tachycardia. Coronary thrombosis, to our surprise, was second, being the exciting factor in 13 per cent. Respiratory infections were third with 11 per cent. Rheumatic fever was the obvious cause in 7 per cent. Pulmonary infarction was the factor in 3 per cent, malignant hypertension in 2, exertion in only 1½, anemia in 1, and thyrotoxicosis in but 0.7 per cent. In a large group of 38 per cent the onset was very gradual with ill-defined or no precipitating factor, quite likely some very minor strain setting off the failure in the case of a myocardium whose reserve was nil; in 5 per cent the onset was very sudden due also to unknown precipitating factor. In only five cases of the thousand could a surgical operation be blamed for the failure. Pregnancy was the precipitating factor in two patients. Trauma was responsible in two and excessive ingestion of fluid in one.

To attempt to discover and appraise the precipitating factor in con-

gestive heart failure is decidedly worth while since we found that "when failure is precipitated by a removable or controllable cause, such as auricular fibrillation, respiratory infection, exertion, and thyrotoxicosis, the patient has roughly a 50-50 chance of regaining some degree of compensation. This is also true of those patients in whom failure occurred suddenly with no assignable cause and it seems likely that here, too, some temporary factor was at work." The prognosis, we found, depended much more on the exciting than on the underlying causes or on the age of the patients, except that those over seventy did poorly. Marked cardiac enlargement carried with it a poor prognosis, regardless of cause. Hypertension was a hazard, increasing the incidence of heart failure in patients with myocardial infarction.

It is, of course, of prime importance, in appraising a case, to determine not only the particular underlying and precipitating factors but to decide and state clearly the degree of structural change from the normal and the severity of the exciting cause. Thus, rheumatic heart disease may be slight with minimal strain from any respiratory infection, never reaching the limit of the cardiac reserve over a long life. On the other hand, extensive myocardial infarction complicating hypertensive heart disease may lead to rapid failure and death. Between these two extremes all grades of strain result in all grades of cardiac enlargement and failure. Some hearts remain competent for many years despite constant strain.

What are the evidences of myocardial failure and what are other conditions that may simulate it? Since at least three-quarters of all cases of myocardial strain have such strain exerted on the left ventricle as the result of systemic hypertension, aortic valve disease, or myocardial infarction, the first evidence of such strain is left ventricular enlargement, and the first symptom to show that the strain is proving to be serious enough to cause pulmonary vascular congestion is breathlessness on effort that had previously not been elicited by that particular effort and which cannot be blamed on some complication like a bronchial infection. The interval of time between the beginning of the development of cardiac enlargement and the onset of this symptom of dyspnea varies from hours in the case of a fulminating large myocardial infarct to a good many years in the case of a slowly progressive systemic hypertension or aortic stenosis. But enlargement there must always be, due to dilatation or to dilatation and hypertrophy, before dyspnea can rightly be

attributed to heart failure. The non-cardiac causes of dyspnea are more numerous than the cardiac and may be wholly responsible even in a cardiac patient, but it is a common experience to find that a non-cardiac cause may itself precipitate failure of the heart, particularly a respiratory infection in winter in an old person with heart disease; in such cases one must use a good deal of skill in determining how much of the dyspnea may be due to the heart and how much to the complicating respiratory infection—special tests of blood-flow velocity can help here.

The dyspnea in mitral stenosis is to be differentiated from that in the case of left ventricular strain and failure from the standpoint of pathogenesis, prognosis, and treatment. As Vieussens indicated so clearly over 200 years ago, this dyspnea is not to be ascribed to heart muscle failure, though it often leads to it, but then of the right ventricle and not of the left. It is common for severe dyspnea, even to the point of acute pulmonary edema, to develop suddenly in a patient with mitral stenosis who had previously been doing well, due to the onset of auricular fibrillation which so often complicates mitral stenosis. The tachycardia, which practically always accompanies auricular fibrillation at first, overloads the lungs with blood and increases pulmonary arterial pressure to the point frequently of causing the right ventricle to fail in its turn; hence it is quite obvious why the error of ascribing the dyspnea in mitral stenosis to heart muscle failure is so often made. There is certainly a failure in the cardiac mechanism but not of the myocardium per se. Fortunately, digitalis which is the drug par excellence for congestive heart failure helps tremendously in these cases by reduction of the heart rate by producing heart block and so relieves the strain on both the pulmonary circulation and the right ventricle.

Dyspnea on effort as the first evidence of congestive heart failure in most cases usually tends to increase without treatment and may eventually be present even at rest, resulting in orthopnea, and often in emphysema; and it sometimes is complicated by asthma, which, as Hope so well pointed out, is a superadded reflex phenomenon, to be called in these cases "cardiac asthma" but not to be considered an essential result of left ventricular failure, even in acute stages. Rarely does the pulmonary edema reach the stage of blood spitting. There may be some blood-stained sputum in the most severe acute cases, but if blood is raised in quantity, it almost invariably comes from pulmonary infarct or infection, the former of which so often complicates congestive heart failure.

Signs of left ventricular insufficiency or failure are somewhat slower to develop than the dyspnea on effort. By the time they appear the condition is fairly far advanced. They include accentuation of the pulmonary second sound, which may in hypertensive cases even equal or surpass the already accentuated aortic second sound, diminution of the first sound, and protodiastolic gallop rhythm at the apex. It is important to note that the gallop may be seen or felt even better than it is heard. There may or may not be a mitral systolic murmur due to mitral valve dilatation; other older murmurs, for example, that of aortic stenosis may be strikingly decreased. The pulsus alternans is a fairly common sign of left ventricular weakness but it is usually not looked for. Roentgen examination in advanced cases shows dilatation of the pulmonary artery and its branches in the lung hiluses and in very serious cases it may reveal pulmonary edema; it may incidentally demonstrate the important and common complication of pulmonary infarction, though such is much more frequent after the right heart fails. Incidentally, rales at the lung bases are an *advanced* sign of pulmonary edema and are much more often due, in my experience, to pulmonary infection, or to unilateral or bilateral infarction, or even to atelectasis.

Cyanosis may result from pulmonary congestion when left ventricular failure is of high degree, but is also to be found when right ventricular failure causes stasis, and indeed without any myocardial failure at all when the lungs are seriously congested in mitral stenosis or otherwise, or when there is local systemic venous stasis due to a local circulatory fault. Many patients with congestive heart failure have no cyanosis at all, except terminally.

Let us turn now to evidence of failure of the right ventricle which most often follows that of the left side, but which may result from mitral stenosis or pulmonary vascular disease without left ventricular strain or failure. Probably the very first evidence, if we look for it, is to be found in engorgement of the liver. The liver can doubtless soak up quite a little blood before the venous pressure is much, if any, elevated or enough to be clearly evident by inspection of neck veins or by elevation of actual pressure readings above the rather wide normal range. Dr. Boyer and I have found, for example, that a very early symptom of right ventricular insufficiency in mitral stenosis is *right upper quadrant abdominal pain on effort*, due doubtless to acute hepatic engorgement, comparable to the acute pulmonary engorgement which causes dyspnea

on effort relatively early in the case of left ventricular sufficiency.

Acute and subacute engorgement of the liver that lasts for days or weeks is common and can be readily recognized because of the combination of hepatic enlargement and tenderness in the case of a patient with serious strain of the right ventricle or with very severe acute rheumatic involvement in early childhood. It may subside quickly or slowly with rest and drug therapy but it may go on to a permanent state of liver congestion lasting for years. Chronic enlargement is most common in cases of mitral stenosis and chronic constrictive pericarditis and in such patients may eventually lead to a variable, though rarely extreme, degree of cirrhosis, justifiably called cardiac cirrhosis of the liver, but different from Laennec's, although not long ago it was suspected (but not proved) that some or all of the cirrhosis in rheumatic heart cases might be the result of an acute rheumatic hepatitis. It is natural that the liver rather than the systemic veins should bear the brunt of evidence of right ventricular failure or constriction, and show congestion earlier and often more severely, because of the low pressure in the portal and hepatic circulation and because of the angularity of the entrance of the hepatic veins into the inferior vena cava (along with the effect of gravity).

There are two other points of particular interest concerning the liver in congestive heart failure. The first concerns its pulsation. It used to be thought that a vigorous liver pulse indicated tricuspid valve disease with stenosis; Mackenzie was one of several who exploded that idea. It may, to be sure, and in fact often does, accompany tricuspid valve disease with regurgitation, but when well marked it is of course due to tricuspid regurgitation whether the valve itself is damaged or not. In fact it is now recognized that irreversible dilatation of the tricuspid ring, chiefly in cases of severe mitral stenosis, with little or no tricuspid valve deformity, may remain after recovery, in whole or in large part, of the right ventricular myocardium from a state of congestive failure; this circumstance is well and probably best shown by vigorous systolic pulsation of the deep jugular veins. The liver may pulsate whether or not the heart rhythm is normal, but auricular fibrillation is most often found in such cases and then the liver pulse is a single wave, the ventricular type, as Mackenzie used to call it. Undoubtedly the liver actually pulsates in most cases but in a degree that cannot clinically be recognized in the majority.

The other important observation about the congested liver is that

when a large pulmonary infarct is superimposed, as not rarely happens, there appears a jaundice usually of slight degree, but once in a while more pronounced, due to the inability of the congested liver to take care of the hemolyzed blood pigment from the infarct; and this may cause undue concern about the biliary tract. Such jaundice is always an important sign, however, and if pronounced, is serious.

Next in importance as a sign of right ventricular failure or constriction or of irreversible dilatation of the tricuspid valve or tricuspid valve disease is increased pressure and pulsation in the systemic veins, best noted in the jugulars but occasionally widespread over the body. In cases where the systolic pulsation is marked, there is a very appreciable pulse pressure in the larger veins, consisting in the neck for instance of several centimeters between systole and diastole. The more the engorgement, the less the visible pulsation; hence in most cases of congestive failure the venous pulse is much better seen with the patient upright than in the recumbent position. One other observation about the venous pulse is of special interest and that is the occasional error that may be made in confusing the deep systolic jugular pulse, that actually raises the sternocleidomastoid muscle, with a vigorous carotid pulse. It is easy to avoid this error by observing the sustained character of the venous (c plus v waves) in contrast to the arterial pulse, and by its easy obliteration by relatively light pressure over the jugular bulb. The possibility of this error was pointed out many years ago by Lancisi and, later, by Mackenzie, but is not yet recognized by the large majority of medical observers.

The third sign of right ventricular failure or constriction is dependent edema, of the feet and legs in the upright position, of the lower back and abdominal wall when supine, and of arm and even thorax and one side of the face when lying on one side. Its degree varies tremendously not only with the degree of hydrostatic pressure secondary to the failure of the heart but also with the presence of complicating factors, the most common of which are local obstruction to the venous flow as in cases of varicose veins and thrombophlebitis, and hypoproteinemia in cases of malnutrition. In fact, in some patients without any heart disease at all these other conditions are confused carelessly with congestive heart failure and treated by giving digitalis; in my experience local venous obstruction is often so misinterpreted, malnutrition rarely. Nephrotic edema is also rarely confused with congestive heart failure.

Hydrothorax is an occasional congestive phenomenon in right heart

failure, not in left, and it happens that it is almost invariably right sided at first or entirely. If there is isolated or preponderant left hydrothorax one should look for a complicating factor of pulmonary and pleural infarction or infection; in fact, such may be a hidden cause even in cases of congestive heart failure with right or bilateral hydrothorax.

Ascites is also an occasional congestive phenomenon, usually in advanced dropsy, but also in cases of chronic constrictive pericarditis and mitral stenosis in which the portal circulation has been long obstructed. In some cases of the former condition, that is, constrictive pericarditis, there may be in the subacute or transitional stage an actual peritonitis as a part of the polyserositis, and responsible for some, at least, of the ascites; in most cases, however, there is no peritonitis to give rise to ascites or frosting of the liver—in such patients, the portal obstruction is wholly responsible for the ascites.

One other sign of right ventricular weakness and failure which has been inadequately referred to except by the French school is a diastolic gallop rhythm, maximal not at the apex, as in the case of left ventricular weakness, but over the main body of the right ventricle and so best noted at the left of the midsternum. The most striking instance of this sort that I have ever encountered was in a patient with chronic constrictive pericarditis whom we recently found in a greatly improved state a few months after pericardial resection. His right ventricle had been decorticated and was seen to be beating directly under the skin and soft chest wall tissues (the ribs had been removed over it). It was still obviously atonic and flaccid in diastole, although the systolic retraction seemed fairly vigorous. There was a marked protodiastolic gallop, much better felt and seen than heard, a circumstance commonly found in gallop rhythm but not to the degree noted in this particular patient.

By fluoroscope in right heart failure the superior vena cava may be seen to be engorged and pulsating, but this is not important, for in such cases the jugular pulse is easily detected anyway.

What can we say about other evidences of or tests for congestive heart failure? Help from the x-ray I have already mentioned: There is always a large heart and the size may or may not materially change under observation, growing larger during the failure and smaller again when the myocardium has recovered its tone; in failure of the left ventricle engorgement of the pulmonary circulation is an important sign

and evidence of this in dilated pulmonary arc and lung hilus shadows is one of the chief reasons why roentgenology is a very useful adjunct in the study of heart disease; we don't need its help when the right ventricle fails.

Electrocardiography affords us little or no information of value in congestive heart failure except to tell us which ventricle may have been preponderantly under strain previously and to aid in following digitalis therapy; the prolongation of systole, as measured electrocardiographically, if it really occurs at all in congestive heart failure, is so slight as to be unimportant.

The estimation of the vital capacity of the lungs is not very important; it gives us, however, something of a quantitative figure in following the progress of an individual case which may be quite evident by clinical inspection. For diagnosis it must be interpreted with great caution because of the various other conditions besides congestive heart failure which may affect it.

Studies of the velocity of blood flow are also usually unnecessary, but they do have a place in doubtful cases, for example, in helping to decide whether dyspnea and asthma are due to left ventricular failure or to pulmonary disease or bronchiolar constriction; there will be a delay in all the tests from venous to arterial circulation if congestive failure is responsible for symptoms and signs.

Blood and urine examinations are not important except to reveal the degree of anemia that may be an exciting factor of heart failure, or the presence of leukocytosis in the case of suspected complication of infarction or infection, or of hypoproteinemia as a factor in the causation of edema, or urinary findings of renal disease. Albuminuria is, however, a common, in fact usual, accompaniment of congestive failure of the right ventricle.

I would add a brief word about fever before leaving the subject of diagnosis. It is quite likely that a slight rise of rectal temperature above normal, up to a degree or a trifle more, may occur in congestive failure of the right ventricle because of the difficulty in dissipation of heat from the edematous body with its faulty circulation, but any appreciable fever is to be attributed always to some important complication generally in the form of infarction (particularly pulmonary), or infection (particularly pulmonary or acute rheumatism). Dr. Kinsey and I found that every one of fifty consecutive cases of congestive failure that came

to autopsy showed at least one complication that could account completely for the fever that had been present often for some time before death, although during life it was often difficult or impossible to prove the presence of any such complications. Also it was apparent that the complication was the last straw, none of those fifty patients dying of the congestive failure alone.

What is the prognosis of congestive heart failure? Usually bad, if failure of either ventricle is easily diagnosed and not rapidly cleared after the subsidence of some excessive strain such as a very rapid heart rate in auricular fibrillation. If congestion occurs with little provocation, the future outlook is especially poor, although even here modern therapy may prolong life for a year or more.

When, however, pulmonary congestion is the result of mitral stenosis and not of left ventricular failure, and systemic venous stasis is due to chronic constrictive pericarditis or to a considerable degree of tricuspid stenosis or irreversible tricuspid dilatation, then life may last for many years, restricted to be sure, but often surprisingly comfortable.

It still remains the rule in congestive failure as otherwise, that "the larger the heart the worse the future," save for infrequent exceptions.

In closing I shall present a few pertinent remarks about treatment of congestive heart failure, the principles and details of which are so well covered in current textbooks and journals that they do not need repetition here. Digitalis, in any one of numerous effective forms, still remains the drug par excellence for myocardial failure, no matter what the heart rhythm, although the results are more spectacular in the presence of auricular fibrillation with rapid heart rate. We should, however, be quite sure that dyspnea or edema is of cardiac origin and not due to pulmonary disease or local stasis before we give it; this seems an obvious rule and yet I find it disregarded frequently, even in the best of clinics. Nor is digitalis of value when congestion is the result of chronic constrictive pericarditis unless auricular fibrillation has occurred as a complication to speed up the heart rate, in which circumstance it does help a lot. Also, it is of more than academic importance to avoid giving enough digitalis to upset the patient, inasmuch as the drug will probably be needed during the rest of the life of that individual and should not early be made excessively distasteful. Almost every instance that I have ever encountered of so-called sensitiveness or idiosyncrasy to digitalis is merely the result of physical or mental repugnance due to previous toxic dosage;

it is hard to combat this or to conceal the unpleasant taste although with persistence such difficulties can be overcome. I myself have never met an instance of true allergy to digitalis. There are three other observations about digitalis that I would add. The first concerns the occasional drug intoxication that immediately follows a vigorous diuresis by mercurial injection and which has been wrongly attributed at times to the diuretic; in such cases evidently a good deal of digitalis as well as water may be released quite suddenly from the tissues and hence it is well not to induce a very high saturation by digitalis. The second point concerns the different strengths of the digitalis preparations on the market in recent years. Many were increased in strength to accord with the international standard as recommended by the U. S. Pharmacopeia of 1936, the XIth Edition, while others have retained their old strength on which most of us have based our routine dosage for many years. Since the new potency is from 30 to 50 per cent stronger than the old, it behooves us always carefully to note the statements on the labels of the preparations we are using to avoid the possibility of disagreeable or even dangerous digitalis intoxication which I have found to have become, quite abruptly, increasingly frequent throughout the country in the last few years because of the general lack of appreciation of this important fact. The third point concerns the use of digitalis in modest dosage, say at the rate of one or one-half the usual daily ration without digitalization first, in cases of considerable myocardial strain and enlargement before the muscle fails, in order to prevent congestive failure. Dr. Henry Christian advised this some years ago and I believe that it is a wise move, despite the difficulty of proof of its efficacy.

I have but a word concerning the use of diuretics. Quite rightly the mercurials given intravenously have assumed an important and very useful role in the last decade or two, but there has arisen some neglect of the milder diuretics that may be taken by mouth and which may suffice as adjuvants to therapy by rest and digitalis.

Finally, I would urge the most careful attention to all the finer details of treatment—avoidance of nervous excitement and irritation, an atmosphere of quiet cheerfulness, a simple but adequate and tasty diet of small meals, limited salt and fluid intake and as few medicines as possible. Where life and comfort hang in the balance one cannot neglect a thing. Therefore, even though heart failure is the last stage of heart disease and, hence, not the most important, it is one of our impelling tasks, as physicians, to combat it as long as we can and to ease the sufferings of its victims.

ARTERIOSCLEROSIS: SOCIAL SIGNIFICANCE AND RECENT ADVANCES IN TREATMENT*

GEORGE MORRIS PIERSOL

Professor of Medicine, Graduate School of Medicine, University of Pennsylvania

A CONSIDERATION of the social significance of arteriosclerosis requires some definition of what is to be included under the omnibus term, arteriosclerosis. This common heading usually is applied to three different lesions. The first is atherosclerosis, the nodular type of vascular degeneration that affects chiefly the aorta and its branches but is also found in certain small arteries, particularly the coronaries and cerebral vessels. Although the exact cause of atheroma is unknown, it is generally conceded that it is a degenerative process of advancing years, which may or may not be associated with high blood pressure. The second type is the medial sclerosis of Mönckeberg. This form is seen particularly in the medium sized muscular arteries, particularly those of the extremities. Tortuous temporals and the pipestem radials are well known and common examples of this type of vascular disease. It bears no relation to high blood pressure, is found in older people and must be looked upon as a senile degenerative change. The third type is diffuse hyperplastic sclerosis which attacks the small arteries, is seen best in the arterioles of the kidneys and is intimately associated with hypertension. The condition has been well termed arteriolarsclerosis. It differs from the first and second types in that it is not primarily a degenerative change of old age. It is frequently encountered in younger people and is regarded by some as the reaction of the smaller arteries to the strain of prolonged high blood pressure.

With the exception of the last group, it is evident that the vascular lesions commonly referred to under the term arteriosclerosis, are intimately associated with the process of ageing and are encountered chiefly in individuals of the upper age groups. Although numerous examples of arteriolarsclerosis are observed in young people, the majority of individuals suffering from this form of vascular disease have attained to the

* Presented October 14, 1941 at the Graduate Fortnight of The New York Academy of Medicine.

later decades of life. It seems not unreasonable to suggest therefore, that there is a relationship between the vascular processes generally referred to as arteriosclerosis and growing old.

The present state of our knowledge makes it unjustifiable to state that age is the cause of arteriosclerosis or conversely, that arterial degeneration is the cause of old age. Winternitz and his associates are disinclined to regard arteriosclerosis as "primarily degenerative or the inevitable concomitant of age." There are others who disagree with this viewpoint. Alfred Cohn, for example, raises the query, "may not the inevitable concomitant of age be vascular change?" It is common experience to observe individuals who have attained far advanced years without exhibiting any evidences of arteriosclerosis. Conversely, many young people are encountered who have prominent signs of vascular degeneration. It may well be as William Boyd puts it: "The advance in years merely permits some slowly acting cause to produce the effect on the vessels." The oft quoted classic remark of Sir William Osler that "a man is as old as his arteries," still has much to commend it.

The relationship of arteriosclerosis to ageing involves the consideration of a problem that has long engaged the interest of outstanding philosophers and biologists. Is old age an involuntary phenomenon physiological in nature or is it disease? The most satisfactory discussion of this fundamental problem is to be found in the scholarly treatise on *Old Age* written some years ago by the late Aldred Scott Warthin. He pointed out that from embryonic life until death the processes of involution are constantly active and that the primary tissue changes observed in these involuntary processes are identical with those characteristic of ageing. Warthin groups the primary tissue changes of senescence under four heads: 1, numerical atrophy, the result of the gradual loss of power of cells to divide; 2, quantitative atrophy, the reduction in the size and number of parenchymatous cells; 3, shrinking and condensation of intercellular substance; 4, vascular changes, particularly vessel collapse and obliteration of lumen. These changes are inherent in the organism, inevitable and physiological, and, if undisturbed by environmental factors or disease, finally lead to failure of vital functions and biologic death. In the vast majority of individuals these primary involutionary processes are accelerated or modified by secondary pathologic changes of which those secondary to vascular lesions such as arteriosclerosis, with its attendant phenomena of thrombosis, embolism,

hemorrhage and atrophy, occupy a conspicuous place. It is these secondary pathological conditions that prevent most senile individuals from attaining their full life span. They embrace the causes of death which occur during the last third of life of which those due to degenerative vascular disease come first. A survey of the various causes of death at different ages for the general population of the United States emphasizes this. A little over 25 per cent of all deaths between the ages of 40 to 50 are due to cardiovascular conditions. The proportion of deaths due to this form of degenerative disease mounts steadily thereafter with each decade until between the ages of 80 to 89 it accounts for two-thirds of all deaths.

The adoption of such a conception of the mechanism of ageing is helpful in explaining the marked individual variations that are commonly observed in the rate of ageing and the symptoms of senility. Those in whom the intrinsic senile process progresses in an orderly fashion, uninfluenced by secondary pathologic changes and little affected by unfavorable environmental factors such as malnutrition, fatigue, trauma, infections and intoxications, may attain a ripe old age characterized by unusual mental and physical vigor. In this group are embraced the many outstanding examples of men and women who, in spite of extreme old age, have retained their creative ability and have accomplished some of the world's greatest works. On the other hand, there are those who, before they reach the age of 60, an age arbitrarily adopted by many gerontologists as the time at which old age begins, exhibit the physical and mental characteristics of advanced years. It is the secondary pathological changes rather than the essential age process itself that is responsible for the clinical manifestations of ageing in this group. It is Warthin's conviction that sclerosis of the arteries with its resultant effect upon the circulation and nutrition of organs becomes a chief collaborative factor in hastening or exaggerating the parenchymatous involutions of senescence, clinically recognized as premature age, and that the converse condition, deferred age, comes from the absence of any marked degree of arteriosclerosis. From the foregoing it seems not illogical to conclude that there is such an intimate association between arteriosclerosis and ageing that their social consequences are inseparable and for all practical purposes may be regarded as identical.

Acute disease, except when it occurs in epidemic form, has no broad social application. Its effect, regardless of how disastrous that may be, is

restricted largely to the individual and to those with whom that individual is in close social or economic contact. Such, however, is not the case when we consider a chronic disease of widespread and practically universal occurrence, of long duration, insidious and progressive in its course. Arteriosclerosis falls in this category.

The obvious social consequences of arteriosclerosis are those associated with the disabilities that occur as the result of its various serious sequelae, such as cerebral hemorrhage and thrombosis, myocardial failure, coronary occlusion, renal insufficiency and the different manifestations of cerebral degeneration grouped under senile dementia. In those in whom primary hypertension is the antecedent condition, some of these catastrophies may occur at a relatively early age, suddenly striking down individuals at the height of their productivity. For the most part the changes are insidious and their effects do not become apparent until the later years of life. In either event the social and economic results are the same. Those so afflicted, become incapacitated to a point where their earning power is lost or at least impaired. They become a burden upon their families and frequently, in the end, a charge upon the State. The amount of money involved in lost wages and the actual cost of their medical care and maintenance is difficult to estimate but it is plain that the annual cost runs into a huge figure which directly or indirectly must be borne by the wage earners of the nation.

The more remote and less apparent significance of arteriosclerosis presents much more important and far reaching consequences of social, economic, and political import. A proper understanding of these aspects of the subject demands some inquiring into the problems which have arisen as the result of the changing trend in the age composition of our population.

It is hardly likely that arteriosclerosis presented a serious social problem in the days of the Roman Republic when, it has been estimated, the mean length of life was between 20 and 30 years. The same was undoubtedly true in the early days of this country, for at the time when the Declaration of Independence was signed, life expectancy had reached only 35.5 years. By the turn of the century in this country, longevity had reached 50 years. From that time on life expectancy has steadily increased. By 1930 it was 60 years, at the present time 3 or 4 years have been added to this and it is estimated that within a few more decades it is reasonable to expect the span of life to have increased to 75 years.

It is interesting to note that this gain in life expectancy has occurred largely during the earlier years of life. By 1931, the expectation of life at birth in white males had risen to 58.84 years, whereas during the active years of middle adult life the increase in longevity has only been about one year. In the later decades of life, practically no gain has occurred. It is evident that this prolongation of life is limited largely to the younger age groups. As life expectancy has increased, the mortality in the first 10 years of life has notably decreased with no corresponding increase in mortality in the higher age brackets. These changes have resulted from improved control of the various infectious diseases, the virtual elimination of certain epidemic diseases, marked lessening of infant mortality, improved public health programs, a better understanding on the part of the people as a whole of the problems of diet, nutrition and personal hygiene, as well as a lessening of fatal accidents. Couple with this the fact that the birth rate of the United States is steadily declining, from 30 per thousand in 1900 to 16 per thousand today, it is easy to understand why the age composition of our population has undergone such a radical change which has brought about a startling increase in the number of older people. Further study of the age composition shows that whereas about one hundred years ago 52.5 per cent of the total population was under 20 years of age, today only 36.7 per cent fall into this group. Coincidentally the number of individuals aged 65 or over has increased. The middle of the last century they made up only 2.6 per cent of the total population, they now represent over 6 per cent and it has been conservatively estimated that in approximately another fifty years, more than 40 per cent of the entire population of this country will be 45 years of age or older.

With this amazing age increase comes a marked increase in the so-called degenerative diseases of which arteriosclerosis and its various sequelae occupy a commanding position. This is further emphasized by a study of the principal causes of death during the last 50 years which shows that the rate per hundred thousand of the various degenerative diseases has steadily risen whereas death from preventable diseases has undergone a conspicuous decline. Cardiovascular disease, which was fourth among the causes of death in 1900, now occupies first place. This is further borne out by the observations of Barker, who carried out complete clinical studies on a group of 300 new patients aged over 60 years. The diagnostic findings showed that cardiovascular disease was

by far the most common disorder in those between 60 and 70 years. The same was true in the older group of patients. As Christian has pointed out in a discussion of what he calls the non-preventable diseases, preventive medicine has saved life chiefly among the young thus enabling them to attain older years and to become the victims of degenerative conditions in the end. One significant result of the triumphs of medicine has been to bring about a material increase in the number of old people in our nation, thereby creating social and economic problems which cannot be ignored. In order to meet these increasing responsibilities adequately, it is essential that we show a greater interest in acquiring a better understanding of the psychological, social and economic needs of this increasing group of ageing arteriosclerotics in our midst.

Few people anticipate approaching old age with any degree of satisfaction. Many violently resent growing old and refuse to accept with equanimity their declining powers and increasing limitations. Examples of this mental attitude are the traditional disinclination of older women to admit their age and the resentment shown by so many patients when they are told that their symptoms are but the evidence of advancing years. This feeling of resentment against the inevitable, and this morbid dread of growing old is a source of much unhappiness and discontent among older people which is not infrequently reflected in unfortunate sociological consequences both in the home and in the community. It is not so much death that is feared by old people as the lurking dread of prolonged illness, a long period of idleness and even uselessness after a life of activity, and the loss of economic independence. It is the feeling of inadequacy, the thought that they are no longer essential and a lack of confidence in their ability to adjust themselves to changed conditions that are such disturbing factors to them. Continued advance in medical science will doubtless do much to lessen the suffering of the aged and to mitigate more and more, their physical handicaps. Improved medical care however, is not enough. It is the social aspects of the problem of growing old that must be solved. A means must be found to educate people to plan for their later years. Such a plan must involve more than an effort to accumulate enough money to sustain them in old age, although it is true that the assurance of economic security adds in no small degree to the peace of mind of those approaching senescence. This is well realized and has been given concrete expression in the social security and old age pension acts that have been instituted by the Fed-

eral government and many States. Although these pensions will to some extent meet the needs of the poor, they are obviously inadequate to allow most old people to live at the social and economic levels to which they have become accustomed and upon which their contentment depends to a considerable degree. There is a tendency to expect old people to accept compulsory retirement along with the dole. Such an attitude is both unfortunate and unsound sociologically and psychologically. The best insurance against unhappiness in old age is to be found in *occupation.* It is clearly the duty of society to educate older people to expect to make every effort to help themselves. The problem of providing useful occupation for this ever increasing group should be given careful study. They should not be asked to compete with youth or to labor with the same intensity that characterized their more active period of life. The present appalling situation with its wanton destruction of youth and the diversion of large numbers of young workers from productive occupations, furnishes illuminating examples of the effective ways in which the older element of a population, when necessity arises, can be occupied to advantage. E. V. Cowdry well sums up this aspect of growing old when he states, "The most effective preparation for advanced years is cultivation of some line of activity which can be carried on as we become more and more physically feeble. The really happy aged person holds his head high, consequently avoids a feeling of inadequacy because he or she is able to do something extremely well. It makes little difference what this something is as long as its value is apparent."

One of the most important problems connected with the social consequences of ageing, is the question of retirement. In an earlier generation when old people were much fewer in number, age was looked upon as a distinction. Today, in a social order which glorifies youth, it is held a liability. The current belief that after middle life enterprise, productivity, adaptability, and originality must decline has been widely accepted in both the professions and industry. The executive must leave the desk from which with wisdom and foresight he has directed a vast industry; the surgeon, at the height of his best clinical judgement, is forced to turn his back upon the hospital; the teacher, when his knowledge and intellectual powers have ripened into full fruition, finds the door of the classroom closed to him; all because society, still repeating the words of the Psalmist, "the days of our years are three score years and ten,"

written at a time when life expectancy was little more than 20 years, is convinced that at the arbitrary age of 65 the powers of all men must fail. There is no scientific evidence to show that there is any single age at which human beings of necessity experience significant loss of mental power. Activity of mind or body does not wear a man out except as it is influenced by environmental states such as accident, disease, malnutrition and discouragement. To be forced by retirement out of the active affairs of life, especially when one still retains a lively interest in and the ability to perform those accustomed duties, is one of the greatest shocks that can come to most individuals. When the stimulus of responsibility is withdrawn, the urge to effort ceases. Few individuals can successfully survive the inactivity of retirement. When the average man feels his usefulness is ended, the debilitating effects of old age come on apace. There are obvious reasons why it seems desirable to those who control our industries as well as our varied institutions to insist upon compulsory retirement at a given age. It affords opportunity for the advancement of younger men, makes room for the employment of others and introduces the vitality and fresh viewpoint of aggressive youth. It is unfortunate that retirement has to be placed upon such an arbitrary basis. It would probably serve the best interests of the individual, industry, and the community if some discrimination could be used so that those who, by reason of their experience possess exceptional judgement and administrative ability might be retained in some capacity of usefulness. The problem of the increasing millions of elderly persons who must and should have an opportunity to work is serious and calls for the wise and thoughtful consideration of our best minds.

Stieglitz has recently pointed out that industry is becoming acutely aware that the average age of their employees is increasing at a surprising rate and this in spite of the fact that a large number of unemployed existed until recently. The situation is becoming more acute as the present emergency creates a shortage in trained personnel and diverts many young men to the armed services of the country. It seems apparent that some means must be found by which older employees may be retained and productively employed in jobs suited to their capacity, so that their independence may be preserved and the value of their skill and experience not wholly lost to industry.

The question of increased retirement coupled with the steady rise in the age of our population is bringing about an economic and political

dilemma of far-reaching implications. It is a matter of record that during the last 75 years, the birth rate in this country has steadily fallen, there has been a relative decrease of children under 5 years of age and the relative number of persons over 65 has almost doubled. During this same period of time, the productive element of the population, aged between 20 and 44 years, has remained constant. Upon this latter group falls the chief burden of caring for the young and dependent older people. Child labor legislation, more time devoted to education and enforced earlier retirement of older workers is steadily diminishing the group of available productive workers, who find themselves confronted with the increasing responsibility of providing for the young on the one hand and an increasing number of non-producing older people on the other. It follows, therefore, that a dwindling group of producers is being called upon to provide for all the rest. In order to relieve the productive element of the population from this increasing burden, the government attempts to assume some of this responsibility. Such measures of social security, commendable as they may be, can only be provided for by increased taxation which in turn falls upon the industries and individuals that employ labor. In order to meet the needs of the non-producers, taxation is gradually being increased to the point where profits are eliminated thereby creating an unbalanced situation which involves conflict between the interests of producers and consumers.

This paradoxical situation has been graphically stated by Mark Sullivan who points out that although in the next 25 years the increase in the total population of the United States will be comparatively small, the increase in the number of old people will be rapid and great. Those aged over 65 will have increased approximately from 46,000,000 to 60,000,000; meanwhile, the number of productive workers aged between 20 and 65 will have remained about at their present level, around 80,000,000. This last class will be called upon to support, either privately or through taxation, a materially increased number of young nonproductive individuals and a group of old people that will have doubled in number. The productive group of workers will be called upon to pay for the education of the young and pensions for the old. Although the total number of workers remains constant at about 80,000,000, it must be borne in mind that one-half of these are either unemployed or are housewives so that actually only about 40,090,000 producers will be called upon to support an equal number of their own age, plus the

increased number of young and old non-producers, a total which has been roughly estimated at 116,000,000. The political and economic potentialities of such a situation in which the burden of caring for the old and young will directly or indirectly be placed upon the productive workers of this country are far-reaching and to say the least, disquieting.

Aside from its economic aspects, there are definite political implications connected with this steady increase in the older element of the population, particularly if they are taught to expect early retirement and financial aid from the State. Such a group could readily become a pressure block of extreme political significance. If as a public policy we force this group of older individuals into idleness, we run a definite risk of placing American politics under the control of the senescent. Conservatism, caution and inflexibility are psychological characteristics of old age. The question has been raised whether democracy as we know it will continue to be as effective while our voting majority advances in age. Roy Helton has said that it will not be safe for America to permit the present psychology of old age to dominate even a powerful minority of our citizens. The situation has been aptly expressed by Professor John Dewey who writes: "Conservatism increases with age so that in the degree in which the older group expresses itself politically, we have the curious and indeed ironic condition that at just the time when measures of social readjustment are most needed, there is an increasing number of those whose habits of mind and action incline them to resist policies of social readjustment."

The increased incidence of degenerative diseases such as arteriosclerosis, due to the fact that more and more of the population are surviving to old age, is having and will continue to have a distinct influence upon medical practice. There is a growing demand upon physicians to meet adequately the medical needs of our ageing population. In order to do this successfully it is essential that we should acquire a better understanding of the altered physiology and psychology of old age, and the pathological processes peculiar to that period of life. Beginnings along these lines should be made in our medical schools where geriatrics should receive the emphasis that is warranted by its growing importance. As an ever increasing number of preventable diseases are brought under control, the non-preventable, degenerative conditions, notably diseases of the vascular system, are destined to make up the bulk of the physician's practice. Today this is already the case, at least,

in so far as concerns the internist.

In order to cope successfully with this changing trend in the practice of medicine, it is desirable that physicians should develop a more lively interest in and a better understanding of the problems of old age. Until recently, physicians, as a whole, have approached the degenerative diseases of later life in a defeatist attitude that has been as devoid of inspiration to the doctor as of comfort to the patient. Granted that diseases which are the result of degenerative change, such as arteriosclerosis are inevitable, and incurable, it is nevertheless incumbent upon the physician to approach their management in a spirit of greater cheerfulness and optimism. This is justified by the fact that if we will but make an earnest effort to acquire a better knowledge of the psychological and physiological needs of the aged, it is possible not only to prolong life but to relieve suffering, and restore to some degree physical and mental well-being that will do much to mitigate the handicaps and infirmities of age.

There is no condition characteristic of old age that is more deserving of our best therapeutic efforts than arteriosclerosis. Unhappily at the outset we find ourselves seriously handicapped in our efforts to treat this condition because of the lack of knowledge as to cause. The management of a disease of unknown or at best of suspected and multiple etiology, must of necessity be unsatisfactory. It must be conceded that the most effective approach to the control of any disease is its prevention. Of no disease is this more true than of arteriosclerosis. Thus far, unfortunately, in spite of much painstaking study, little has been accomplished along this line.

The most constructive progress that has recently been made looking to the prevention of arteriosclerosis is the work that has been done on what may be termed presclerotic conditions, of which none is more important than hypertension. Although hypertension and arteriosclerosis are in no sense synonymous, and hypertension cannot be said to be the cause of arteriosclerosis, it is undeniable that long continued elevation of blood pressure ultimately is associated with vascular changes due to the strain to which the arterial walls are subjected. This is particularly true in diffuse hyperplastic arteriolar disease. It is not surprising, therefore, that much effort has been directed to devising some method of reducing hypertension, particularly in that group of patients in whom the increased blood pressure is dependent presumably upon arteriolar

spasm and not secondary to chronic renal disease, hyperthyroidism, other endocrine disturbances or heart disease; a group, usually of younger age, suffering from the condition commonly referred to as essential hypertension.

It may be stated that the results of drug therapy in hypertension have been uniformly discouraging. Vasodilators, such as the nitrites, acetylcholine, sulphocyanate, aminophylline, have their place in the treatment of hypertensive paroxysms but are of no permanent value. The continuous use of small daily doses of suitable sedatives, which lower the patient's response to external stimuli, are of more value.

With the failure of medical measures to control hypertension, it is but natural that recourse should be had to surgery. On the assumption that the abnormal increase in blood pressure is the result of disturbances in the sympathetic nervous mechanism, operations have been devised which involve extensive sympathectomy. These include section of the anterior spinal nerve roots from about the 6th thoracic to the 2nd lumbar and section of the major and minor splanchnic nerves above and below the diaphragm. In some techniques partial removal of the adrenal glands has been combined with these procedures. These operative measures have been thoroughly discussed in the literature. From certain clinics have come encouraging reports indicating that in properly selected cases a definite reduction in blood pressure has been obtained which, in some instances, has persisted. The operation is a major surgical undertaking which involves prolonged hospital care and is not without definite risks. At present the results can hardly be said to be so consistently good as to justify its wide application.

A simpler and safer procedure is x-ray therapy, over the adrenals, the carotid sinus and the region of the pituitary. Such a plan has been followed recently by George Griffith of Philadelphia and his associates whose results are as yet unpublished. They have observed a permanent and satisfactory lowering of the blood pressure in an encouraging percentage of over one hundred patients with hypertension who were subjected to x-ray treatment. The plan consists of a series of six properly regulated x-ray exposures followed by an interval of from four to six weeks when it is repeated. Rarely more than two or three series of exposures are necessary to secure persistent and definite lowering of the blood pressure.

The most outstanding work on the etiology of hypertension and the

possibilities of its ultimate control has been that of Goldblatt and his associates who found that the production of renal ischemia, by clamping the renal artery in dogs and monkeys, could produce hypertension similar to that found in man, and that removal of the kidney the renal artery of which had been constricted, brought about a lowering of the blood pressure. It would be inappropriate to discuss this problem now when you are to be afforded an opportunity to hear Dr. Goldblatt on this subject. Suffice it to point out that his observations have focused the attention of urologists on the role that obstructive uropathies and other conditions that may interfere with renal circulation play at times in the production of hypertension. There are now numerous instances on record where removal of such obstruction has resulted in a prompt and permanent lowering of blood pressure. The possibility of such relief should not be overlooked in the study and management of patients who present prearteriosclerotic hypertension.

In any consideration of hypertension mention must be made of the highly suggestive work that is being carried on by Irvine H. Page, A. C. Corcoran and their associates. Their extensive experiments lead them to believe that renin, a protein formed in the kidney, and a renin-activator substance interact and form a third substance which they call "angiotonin." This latter substance is the true humeral vasoconstrictor capable of inducing increased arterial pressure in animals comparable to hypertension in man. They further have shown the existence in the body of substances which inhibit the action of these pressor substances. Other observers, Harrison, Grollman and Williams, have also demonstrated the presence of a humeral antipressor substance which they believe is elaborated by the kidneys. Although this work is still in a purely experimental state, clinical trials are now in progress on the effect of these antipressor substances on patients with hypertension. It would be premature to attempt to evaluate the practical results of these experimental observations, but it is not too much to hope that they will bring us at least nearer to the solution of the all important problem of the cause and control of hypertension.

A second prearteriosclerotic condition in the control of which marked strides have been made is diabetes. The relationship between diabetes and the premature development of arteriosclerosis of the atheromatous type is well-recognized and has been clearly discussed by Warren who points out that diabetics have not only more than their share

of arteriosclerosis but it falls to their lot 10 or 20 years earlier than in the non-diabetic. In the Philadelphia area during the year 1940, there were 913 deaths among diabetics. Of this number 337 died with, but not of, diabetes. This group included 146 in whom death was due to arteriosclerosis and its consequences. More prompt and effective treatment of diabetics, therefore, is another important step in the preventive treatment of arteriosclerosis. Closely allied to diabetes is the question of obesity, the proper control of which is also a valuable factor in the prophylaxis of arteriosclerosis.

Of all the suggested causes of arteriosclerosis there is none that is so well supported by innumerable careful observations and extensive clinical experience as heredity. When Sir William Osler made his oft quoted and somewhat facetious remark that the best way to prevent arteriosclerosis is to choose one's ancestors, he epitomized our knowledge of what is probably the most important factor in its prophylaxis. The hereditary control of such a widespread condition as arteriosclerosis obviously presents insurmountable difficulties. It leads us into the realm of genetics concerning which too little is known and understood by the physician. It is to be hoped that the future may bring to both the medical and the lay public a better appreciation of the far reaching significance of this subject. It is even conceivable that, as time goes on and the State assumes more and more regulation of our lives, some effort may be made toward the control of such conditions as arteriosclerosis by the enforced application of eugenic laws.

There is no subject that has evoked more discussion or that has given fadists greater opportunity than the role played by diet both in the development and control of arteriosclerosis. Much of the blame that has been placed upon diet as a cause of arteriosclerosis is unsupported by adequate scientific evidence. The widespread belief that diets high in protein and salt are responsible for vascular degeneration or for unfavorably influencing its course are ill-founded. It is true that when, as the result of arteriosclerosis, secondary changes are brought about in the heart or kidneys, so that failure of the former or insufficiency of the latter may supervene, a totally different problem is presented. Under such conditions, if the changes in blood chemistry warrant it, restrictions in the intake of proteins, salt and fluid are often necessary. With this phase of the subject at the moment we are not concerned. Attention is called to the fact that in certain types of arteriosclerosis, par-

ticularly those associated with hypertension, in which arteriolar spasm is alleged to be the underlying factor, salt free diets have been advocated by some observers who have claimed excellent results. The procedure is neither desirable nor applicable to arteriosclerosis as a whole. The unwarranted restriction of protein and sodium chloride over a long period of time has been productive of distinct harm to many, inasmuch as it has interfered with their electrolyte balance, impaired their nutrition and increased their anemia. There is more to be said in favor of restricting lipoids in the diet. Experimental evidence indicates that animals fed on diets high in cholesterol show lipoid deposits in the aorta. In this connection, the work of Leary is most suggestive. By feeding rabbits with cholesterol over a long period of time he was able to reproduce with considerable fidelity, the lesions of human coronary atherosis. The results are suggestive though the analogy may not be entirely exact in view of the fact that the metabolism of cholesterol in the rabbit is not identical with that in human beings. In countries in which, during periods of privation, the population had to subsist upon diets that were extremely low in lipoids, the incidence of atherosclerosis markedly diminished. On the other hand, Mallory calls attention to the fact that during the period when diabetes was treated by a high fat diet, there was an alarming increase in the atherosclerosis that accompanies that disease. Within the past 48 hours Professor Lester R. Dragstedt of the University of Chicago has presented experimental evidence to show that the pancreas secretes an hormone called "lipocaic" which enables the body to utilize fats, and that absence of this hormone plus a high fat diet produces experimental arteritis.

The effect of diet on longevity and the degenerative diseases of old age has been made the subject of a special study by Sherman. He holds that nutrition is a factor of equal if not of greater importance than heredity in the question of longevity. Sherman believes that if the known facts regarding proper diet are applied not only can the average life span be increased by 10 per cent but some of the degenerative forces within the body can be neutralized. He advocates an optimum diet, not merely an adequate diet and suggests that one-fifth of the food budget be spent for milk and cream, not less than one-fifth for fresh fruit and green vegetables and the remaining three-fifths for bread, butter, fish and eggs.

In the uncomplicated arteriosclerotic who shows no signs of cardiac

or renal failure, the effort should be made to retain a state of adequate nutrition, avoiding always over nutrition. Because of the tendency to anemia so prevalent in many older individuals, the use of liver twice a week as well as iron rich foods and iron, is frequently of advantage. It would be at variance with the spirit of the times to neglect to mention the role of vitamins in the arteriosclerotic's diet. Sherman is insistent that vitamins A and G are essential to the well-being of old people. The vitamins probably most needed and most useful are Vitamin B-complex and Vitamin C which may be given liberally. On theoretical grounds at least Vitamin D should be used with caution because it may prove harmful by increasing calcium deposits in the vascular tree.

Considerable diversity of opinion exists as to the role that infection plays in the production of arteriosclerosis. It is however, a sound therapeutic principle that whenever known foci of infections exist in the arteriosclerotic, they should be removed but in such a way as to induce the minimum amount of trauma and shock. There are those who lay great stress upon the importance of controlling that somewhat vague and ill-understood condition, intestinal toxemia, in the treatment of arteriosclerosis. It is difficult to appraise its significance until our knowledge of the subject is crystallized. It is obvious that adequate and regular elimination from the gastrointestinal tract is highly desirable. On the other hand, the practice of subjecting the arteriosclerotic subject periodically to the ordeal of violent purgation or, worse, to the much vaunted colonic irrigation is open to serious question. There is no adequate or unbiased evidence to indicate that either alcohol or tobacco are factors of etiological importance in arteriosclerosis. There is probably no harm in their continued moderate and proper use if the life habits of the individual are taken into account, and due consideration is given to the kind of a nervous system with which the patient is endowed.

The abortive and ironical efforts at rejuvenation which from time to time have had their enthusiastic advocates scarcely need serious consideration in a discussion of the treatment of arteriosclerosis. All the procedures thus far have failed—a result readily predictable if the pathology of old age is kept in mind. Furthermore, such suggestions are basically unsound, both from a biologic and physiologic standpoint, since they place undue emphasis upon the single factor of sexual activity. Other systems of the body, notably the cardiovascular and nervous sys-

tems are of far more importance in maintaining the health and well-being of ageing individuals. Until rejuvenescence of all the body tissues can be accomplished, attempts along this line are doomed to failure. With the rapid advances that have taken place in endocrinology, it is conceivable that ultimately some success in this direction may be obtained. To date the extravagant claims that have been made are based more upon fiction, than upon fact.

In conclusion, it is evident that although arteriosclerosis is one of the commonest conditions encountered by the physician, it is still one of the least understood. So long as its etiology remains shrouded in uncertainty its treatment will continue to be unsatisfactory. Meanwhile, as one of the outstanding causes of disability in old age, arteriosclerosis presents social, economic and political problems of national scope that dare not be ignored and which continue to challenge the scientific efforts and wisdom of the medical profession.

RECENT STUDIES IN THE PRODUCTION OF CANCER BY CHEMICAL COMPOUNDS; THE CONDITIONED DEFICIENCY AS A MECHANISM*

The Bulkley Lecture

C. P. RHOADS

Director, Memorial Hospital
Professor of Pathology, Cornell University Medical College

ANY discussion of a topic as comprehensive as the chemical aspects of cancer must be limited, in order to avoid confusion, to relatively few phases of the subject. The two most important divisions are: first, the induction of cancer in man and animals by chemicals of known constitution; and second, the biochemical disturbances present in human beings afflicted with cancer of unknown etiology. To provide us with a better understanding of the way in which cancer is produced, it is desirable to correlate the findings in the organism in which we have caused cancer with the findings in the organism bearing a neoplasm of spontaneous origin. Perhaps in this way we can obtain an inkling of the etiology of cancer and very probably only through a knowledge of the etiology can we obtain information which will lead to prevention and cure.

It is desirable, then, at the outset to review briefly our knowledge of the chemical cause af malignant disease. This requires reference to Percival Pott,[1] the surgeon celebrated for his description of Pott's fracture. As you are probably well aware, he also described scrotal cancer in chimney sweeps as a disease of industrial origin, due to contact of chimney soot with the abraded skin of the worker. With the development of the coal tar and chemical industry in the middle and late eighteen hundreds, a mass of clinical information became available by which tar and tar products were established as causative of cancer in man. This clinical supposition was supported by experimental evidence when in 1912 Yamagiwa and Ichikawa[2] produced cancer of the rabbit's ear by the persistent application of gas-works tar. This classic experiment provided in an animal a suitable test object for the carcinogenic effect

* Read March 21, 1941 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

of chemicals, and led to the isolation from tar of pure compounds which were capable of inducing malignant disease (Cook and his co-workers[3]). As soon as these investigators had isolated one such substance, they immediately began to create, in the laboratory, many synthetic compounds structurally allied to it. This was done in an attempt to ascertain what peculiarity of chemical structure was responsible for the pathogenic effect. They found that, whereas no absolute rule could be laid down, most of the active substances produced were composed of benzene rings linked together, and whereas some modifications did not seem to impair activity, others, though very slight, removed completely the effectiveness.

While all this work was going on in other laboratories, an apparently unrelated but actually rather similar study was in progress. Many years ago Leo Loeb[4] observed that the implantation of ovarian tissue into castrated male mice resulted in the production, not only of female breast structure, but also of cancer of the affected breasts. This observation suggested, of course, the hypothesis that some secretion of the ovary played a role in the production in mice of breast cancer. The correctness of this hypothesis was proved with the development, in the laboratories of sterol chemistry, of methods for the isolation of pure sex hormones. By these methods it was shown that the biological effect of the ovary is due to three chemically similar compounds: estrone, estriol, and estradiol.[5] All three were found to be productive of breast cancer in mice, and the effect was in proportion to the relative abilities of the compounds to induce estrus. Moreover, at about the time that these studies were in progress, the establishment by the chemists of the structural formulae of the compounds made clear another significant fact. They resembled distantly in some respects the chemicals which Cook and his co-workers had derived from tar and found to be carcinogenic.

Here, again, the implication was clear. Certain compounds composed of multiple benzene rings, to which the body was exposed, either by external contact or from the processes of its own metabolic activity, possessed the power of causing cancer.

Another equally important fact became apparent from these studies. Not all mice possessed the same susceptibility to cancer produced by the administration of the pure carcinogenic compounds. Indeed, certain strains of mice are entirely immune to breast cancer which results from the administration of estrogenic substance.[6] Furthermore, the strains which are susceptible are the strains which tend to develop breast cancer

spontaneously. The carcinogenic substances of the type derived from tar will induce cancer in almost all strains of mice, but careful breeding experiments show that here, again, there are distinct differences in the susceptibility.[7]

Not only do strain differences exist, but also different species of animals show marked variations in their tendency to develop cancer as a result of exposure to these compounds. Whereas mice are very likely to do so, guinea pigs are much less so, and rabbits almost not all. In the primates, such as monkey or man, neither the synthesized tar constituents nor the sex hormones have been shown conclusively to have produced cancer. This extraordinary difference in susceptibility leads one to consider immediately the possibility that various species and various strains of the same species may differ in the manner in which they handle, destroy or detoxify those substances which have been shown to produce cancer. Obviously, if such a mechanism of detoxification could be shown to exist and the method by which it operates detected, it might be possible so to enhance detoxification that one could render immune an animal or a species ordinarily susceptible. Furthermore, if one could detect the mechanism of detoxification one could test various strains of animals, or indeed man himself, for the ability to effect this detoxification. Thus one would possess two powerful weapons: a method for the detection of the susceptible individual and a method for rendering him insusceptible. Such desirable objectives appeared to warrant a serious study of the manner in which animals dispose of and supposedly detoxify substances of a type which we know to be cancer-producing.

With this aim in view, some years ago at the Hospital of the Rockefeller Institute, Dobriner and I began studies of the manner in which rabbits, rats and mice handle administered carcinogenic substances. We had two very distinct leads. Cook and his associates[8] had made the observation that none of their synthetic cancer-producing chemicals were active if a molecule of oxygen and one of hydrogen, grouped together as a hydroxyl group, were added to the original structure. Boyland,[9] in England, had studied the manner in which animals handled dibenzanthracene, one of the compounds with which Cook had worked. He found that these animals excreted a phenolic, or hydroxylated, dibenzanthracene.

With these two observations at hand, our task was relatively simple. We only had to devise a suitably sensitive method for the detection of

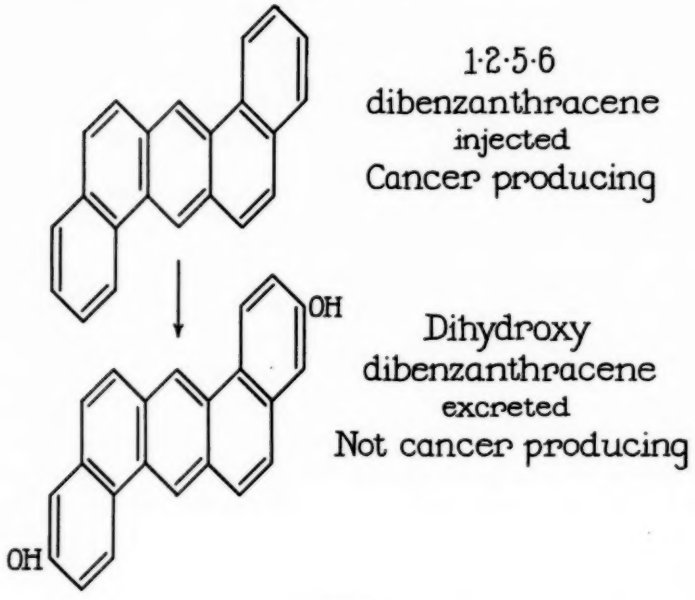

Fig. 1

dibenzanthracene and derivatives of it. With the aid of a grant from the Rockefeller Foundation, it was possible to apply the technique of absorption spectroscopy to this problem.[10] You are probably aware that benzene-like hydrocarbons containing double bonds absorb certain wave lengths of ultraviolet light in a characteristic manner. By this characteristic absorption, it is possible to identify the compound causing it, even though the substance is present in exceedingly low concentration. Such an identification is more specific than any chemical method short of the actual isolation of the compound, and isolation is not possible when one deals with such very small amounts of material as those to which we were restricted. Once our method was perfected and applied, it was possible to show quickly and easily that if we injected dibenzanthracene into a rabbit, the animal excreted a small amount of the substance we injected as well as a large amount of some allied but quite different compound. This was equally true of the rat and the mouse. Furthermore, by chemical reactions we knew that the injected substance contained no hydroxyl group, whereas one or more were present in the material excreted. By the combination of chemical and spectroscopic methods, we

isolated the hydroxy dibenzanthracene into which the rabbit had converted the injected dibenzanthracene and acquired a sufficient amount of this new substance to test its power to produce cancer (Fig. 1). Through the courtesy of Clara Lynch of the Rockefeller Institute, we were provided with twenty-four mice of a strain highly susceptible to the carcinogenic effect of dibenzanthracene. Twelve animals were injected each with 4 mg. of that compound in oil, and twelve littermates of these animals each with 4 mg. of the dihydroxydibenzanthracene. All of the mice which received dibenzanthracene developed tumors at the site of injection, while none of those which received the dihydroxy compound did so. It seemed clear that the rabbit, at least, converted dibenzanthracene into a non-carcinogenic hydroxy derivative, and hence the conversion could be considered to be a protective one. Only recently a confirmatory study has been published by Boyland.[11] Once the fact of a protective conversion was established, it became important to ascertain upon what factors it might depend.

We speculated a great deal concerning what role in the conversion might be played by vitamins because we knew that many of the important chemical processes of the body were carried out by enzymes or ferments of which vitamins form essential parts. Furthermore, we suspected that the conversion of dibenzanthracene took place in the liver and we were aware that the liver is rich in vitamins because it is there that the enzyme systems for which vitamins are essential are particularly active and numerous. We immediately attempted to ascertain whether a deficiency of vitamins played any role in the ability of the animal to detoxify dibenzanthracene. Unfortunately, trouble was immediately encountered because our methods, while qualitatively excellent, were quantitatively insufficiently accurate to provide us with unequivocal information.

By sheer good fortune, however, just at that time an ideal experiment came to hand through the work of the Japanese group headed by Kinosita.[12] This investigator had observed that a dye, butter yellow, composed of two benzene rings linked together, regularly caused liver cancer in rats fed a diet composed of unpolished rice and carrot. If liver or yeast was added to this regime, no cancer occurred. Here, clearly, was an experiment in which a dietary constituent rich in its content of the vitamins of the B complex was protective against induced cancer. To what was this effect due? An elaborate series of experiments has been

carried out, and it will not be profitable here to discuss all of them in detail.[13] Certain facts were made clear, however. In the unpolished rice and carrot diet fed by Kinosita, at least two factors are lacking. One of these is a pure vitamin, riboflavin, and the other is a so far unidentified constituent of casein.[14] When these two substances are fed as a supplement to the rice diet, distinct, though incomplete, protection is provided. It is clear, then, that for the first time it has been shown tnat a deficiency of dietary constituents can render animals susceptible to one type of cancer and that supplement with those constituents protects them almost completely.

To ascertain what factor or factors were lacking in the diet of unpolished rice, it was necessary to establish, if possible, the existence of any deficiency in the bodies of the animals susceptible because of the diet. Since the liver is the principal site of action of those chemical systems called enzymes which depend for their activity upon the presence of vitamins in their molecules, it was reasonable to examine the content of vitamins in the livers of the susceptible rats. This was done by Kensler and his co-workers[15] in my laboratory.

A chemical method was available for the measurement of one important vitamin, riboflavin, but no procedure for the estimation of the activities of the enzyme systems in which it functions was at hand. A very small amount of riboflavin was found in the livers of the rats fed the rice diet which rendered them susceptible to liver cancer from butter yellow. Furthermore, the content of riboflavin in the rice was less than is supposed to be the minimum amount required to keep rats in good health. Moreover, the amount of riboflavin excreted by the rats taking the rice diet for a considerable period was very much lower than the amount excreted by normal rats. When the carcinogen, butter yellow, was added to the diets, the animals eating it apparently spilled in the urine their reserve riboflavin. Lastly, as previously stated, the addition of riboflavin with casein to the deficient diet afforded definite, though incomplete, protection against the cancer. In short, from the evidence presented the fact was clear that riboflavin participated in some way in the protective effect provided by dietary supplements, and that its lack played some role in inducing susceptibility to cancer production by butter yellow.

The importance of riboflavin in the etiological mechanism suggested immediately that the vitamin interacted in some way with the chemical

which caused the cancer and perhaps had to do with its detoxification. The validity of this suggestion still remains to be established, although it is still under investigation in my laboratory. The possibility itself, however, warranted a study of the activity, in the livers of the various groups of animals, of the kinetic enzyme systems of which vitamins form essential parts.

As stated before, no method was available for the measurement of any riboflavin enzyme. Dexter, in my laboratory, had developed, however, an excellent and relatively simple procedure for the measurement of the activity of Coenzyme I or diphosphopyridine nucleotide. That enzyme system is concerned with fermentation and depends upon the vitamin nicotinic acid as an essential constituent. Kensler[15] applied this method to the study of the livers of the experimental animals. The results provided particularly significant information. In the rats fed only the diet which makes them susceptible to cancer from butter yellow, the livers showed no decrease in the content of Coenzyme I. If butter yellow was added to the diet, however, a prompt and serious decrease in the amount of the coenzyme occurred. This drop developed long before the malignant new growth was apparent and could not be correlated with simple destruction of liver tissue. The Coenzyme I content of the tumor was even lower than the content of the substance in the adjacent non-malignant liver tissue. On the other hand, if the deficient diet and butter yellow were fed with some protective supplement, such as yeast, perfectly normal liver levels of Coenzyme I were found, and, of course, no cancer occurred.

The observation just described was of considerable fundamental importance. It proved, for one thing, that a liver cell cancer could grow widely and rapidly, apparently well-nourished, even though its content of an essential vitamin, riboflavin, was much lower than was found in normal liver tissue. More striking still, the observations proved that the administration of the cancer-producing chemical interfered in some way with the activity of an enzyme system, Coenzyme I, of which another essential vitamin, nicotinic acid, is a part without which the enzyme will not operate. We were certain that the diets contained adequate amounts of the vitamin and, furthermore, the rat has been shown not to require dietary nicotinic acid to maintain health. Nevertheless, the vitamin in the tissues of the animals used in these experiments was certainly made nonfunctional if butter yellow was fed. In other words, butter yellow

blocked the activity of nicotinic acid in the livers of the experimental rats. Hence, no matter how much free nicotinic acid was available, the livers were in a state of nicotinic acid deficiency as serious as that found in the livers of dogs with black tongue, the analogue of pellagra in man.

It appeared, then, that a "conditioned deficiency" clearly had been established; a vitamin deficiency due, not to failure of the animal to ingest the vitamin, but to some interference with the function of the vitamin in the form in which it is biologically active. The existence of such a "conditioned deficiency" had been postulated previously, but it had not been proved to exist. What implication, then, has the fact that a pure chemical, in this instance the carcinogen butter yellow, had been shown to cause disease, in this instance cancer, by blocking the functional activity of a vitamin, in this instance nicotinic acid? The principle of the "conditioned deficiency" so demonstrated might be applicable to any number of disease processes hitherto poorly understood.

Further proof of the thesis of the "conditioned deficiency" was required. It was obtained as follows: Clearly, the oral administration of carcinogenic butter yellow produced a serious loss of Coenzyme I (the enzyme which contained nicotinic acid) activity in the livers of the treated animals. Hence, an *in vitro* test should be possible, as follows: Butter yellow, or some metabolic product of it, should decrease the rate of respiration of the surviving liver slice, a rate dependent in part upon the function of Coenzyme I. More specifically, and more conclusively, the carcinogen or its metabolites should block, in the test tube, the function of the nicotinic acid-dependent Coenzyme I.

To make the experiment required the isolation and identification of the breakdown products of butter yellow excreted by animals fed that compound. This was done in my laboratory by Dobriner and Stevenson.[16] The chemical steps involved, as discovered by these investigators, are presented schematically in Fig. 2. Amido-phenol and paraphenylene diamine, both free and both acetylated, were isolated from the urine of rats fed butter yellow. These, with the carcinogen originally administered, gave five compounds to test *in vitro* for their effects on the pure Coenzyme I system. These tests were made and very interesting results obtained. Only one of the metabolic products, paraphenylene diamine, inhibited the activity of the enzyme system. The other four were almost wholly inactive.

This observation suggested immediately the trial of dimethyl para-

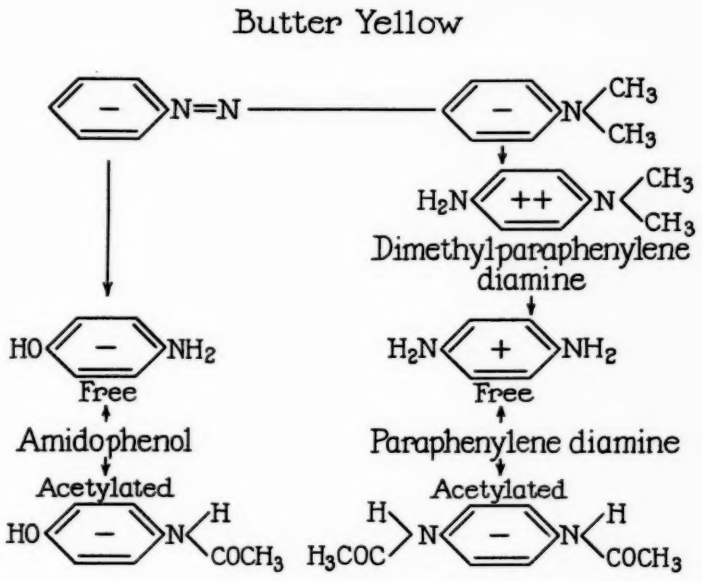

Fig. 2

phenylene diamine which, though not isolated, probably is the precursor in the liver of the paraphenylene diamine formed by the metabolic breakdown of butter yellow in the body. The dimethyl compound was tested and was found to be even more toxic to the Coenzyme I than was the simpler compound into which it is converted. The results of these experiments on the toxicity of the various butter yellow metabolites are presented in Table I.[17] It should be noted that the conversion by the body of the paraphenylene diamine as well as of the dimethyl compound to acetyl derivatives is a detoxification mechanism, since the acetylated substances are completely without toxic effect on the enzyme system studied.

From the experiments just described, then, evidence was provided to substantiate our original assumption. *That is, that the administration of at least one carcinogenic chemical injured normal cells by interfering in some way with an enzyme system which is essential for their normal chemical function and so their normal life.* The results suggested, furthermore, that this principle of the poisoning by a specific chemical of at least one, and possibly more than one, normal enzyme system caused

TABLE I

Effect of Acetylation on Toxicity

System	mm. CO_2 in 1st hour
Control	488
Control and dimethylparaphenylenediamine	78
Control and acetyldimethylparaphenylenediamine	520
Control and paraphenylenediamine	95
Control and mono-acetylphenylenediamine	488
Control and diacetylphenylenediamine	498
Concentration of compounds = 1×10^{-3} molar	

the normal cell to become a cancer cell. An analogy can be drawn, perhaps, to the polycythemia which occurs in human beings as an adjustment to the anoxemia of great altitudes. Even more pertinent, possibly, is the analogy to the mutations which result from the persistent exposure of tissues to such physical agents as x-ray.

If these analogies hold; that is, if some permanent alteration of liver cells is caused by the prolonged poisoning of a normally required enzyme system, and if this alteration is characteristic of the cancer cell, another experiment should be possible. The fact should be demonstrable that the liver cancer cell, produced by the administration of butter yellow and the persistent breakdown of that substance to its derivative dimethyl paraphenylene diamine in the liver, is capable of respiring normally in the presence of a concentration of the dimethyl compound which poisons the respiration of normal cells. This experiment has been done, and the results establish the validity of our assumption. The respiration of a normal liver tissue suspension is inhibited by a concentration of dimethyl paraphenylene diamine which appears to be without effect on the respiration of a suspension of cancer tissue which developed supposedly as the result of the intoxication of normal liver tissue by the same compound. This difference does not hold for liver slice, however, and we have no explanation at present for this fact. In short, the enzymes of the cancer cell can operate in the presence of a compound

which, in the same concentration, is poisonous to the enzymes of the normal cell.

It appears probable, then, that as far as liver cancer is concerned, the malignant cell differs radically, as concerns the chemical systems which make its life possible, from the normal cell from which it is derived. It appears likely, furthermore, that this chemical difference is due to the change required to enable the cell to survive in spite of a chemically induced "conditioned deficiency" disease.

I am sure that the question will be asked immediately, "What bearing have the results of this set of experiments on the cause and cure of cancer in man?" It is not possible to answer this question at the present time. This much may be said, however. The studies suggest the necessity of a careful and precise examination of a large number of patients bearing malignant neoplasms in order to ascertain whether or not they show any evidence of an interference with chemical systems of which vitamins form essential components. Even more important, however, would be studies based upon the evidence presented that at least one type of malignant cell, that of butter yellow liver cancer in the rat, is immune to the chemical which probably causes it to develop.

If evidence of a "conditioned deficiency" in man were obtained, and if we knew exactly upon what alterations it depended, the correction of the disorder, and so the prevention of cancer, might be conceivable. If the second suggestion is confirmed and other types of malignant cells proved to differ from the normal cells of their origin in respect to their resistance to pure chemicals, the road to chemotherapy might be opened.

Both of these hypotheses are wholly speculative at present, and further study may well prove both to be untenable. Until such evidence is at hand, however, it is at least of some interest, and may be of some importance, to speculate about the "conditioned deficiency" and the induction of malignant neoplasms.

REFERENCES

1. Pott, P. *Chirurgical observations.* London, Howes, 1775, p. 64.
2. Yamagiwa, K. and Ichikawa, K. Experimentelle Studie über die Pathogenese der Epithelialgeschwülste, *Mitt. a. d. med. Fak. d. (k.) Univ. z. Tokyo,* 1916, *15:* 295.
3. Barry, G., Cook, J. W., Haslewood, G. A. D., Hewett, C. L., Hieger, I. and Kennaway, E. L. Production of cancer by pure hydrocarbons, *Proc. Roy. Soc.,* ser. B, 1935, *117:* 318.
4. Lathrop, A. E. C. and Loeb, L. Further investigations on the origin of tumors in

mice; on the part played by internal secretion in the spontaneous development of tumors, *J. Cancer Research*, 1916, *1:* 1.

5. Doisy, E. A. The ovarian follicular hormone, in *Female sex hormones*, University of Pennsylvania bicentennial conference, Philadelphia, Univ. of Pennsylvania press, 1941, p. 1.
6. Gardner, W. U. Influence of estrogenic hormones on abnormal growths, *Science*, 1937, *85*, Suppl. No. 4: 67.
7. Lynch, C. J. Studies on the relation between tumor susceptibility and heredity; inheritance of susceptibility to tar-induced tumors in the lungs of mice, *J. Exper. Med.*, 1927, *46:* 917; and Susceptibility of mouse strains to lung tumor and sarcoma induced by 1:2:5:6-dibenzanthracene, *Proc. Soc. Exper. Biol. & Med.*, 1935-36, *33:* 401.
8. Cook, J. W. and Kennaway, E. L. Chemical compounds as carcinogenic agents; first supplementary report: literature of 1937, *Am. J. Cancer*, 1938, *33:* 50.
9. Levi, A. A. and Boyland, E. The production of dihydroxy-1:2:5:6-dibenzanthracene by rabbits, *Chemistry & Industry*, 1937, *15:* 446.
10. Dobriner, K., Rhoads, C. P. and Lavin, G. I. Conversion of 1:2:5:6-dibenzanthracene by rabbits, rats, and mice; significance in carcinogensis of this conversion, *Proc. Soc. Exper. Biol. & Med.*, 1939, *41:* 67.
11. Boyland, E., Levi, A. A., Mawson, E. H. and Roe, E. Metabolism of polycyclic compounds; production of a dihydroxy-1:2:5:6-dibenzanthracene from 1:2:5:6-dibenzanthracene, *Biochem. J.*, 1941, *35:* 184.
12. Kinosita, R. Studies on the cancerogenic azo and related compounds, *Yale J. Biol. & Med.*, 1940, *12:* 287.
13. Sugiura, K. and Rhoads, C. P. Experimental liver cancer in rats and its inhibition by rice-bran extract, yeast, and yeast extract, *Cancer Research*, 1941, *1:3*.
14. Kensler, C. J., Sugiura, K., Young, N. F., Halter, C. R., Rhoads, C. P. Partial protection of rats by riboflavin with casein against liver cancer caused by dimethylaminoazobenzene, *Science*, 1941, *93:* 308.
15. Kensler, C. J., Sugiura, K. and Rhoads, C. P. Coenzyme I and riboflavin content of livers of rats fed butter yellow, *Science*, 1940, *91:* 623.
16. Dobriner, K., Stevenson, E. S. and Rhoads, C. P. Studies on the metabolism of dimethylaminoazobenzene, *in preparation.*
17. Kensler, C. J., Dexter, S. O. and Rhoads, C. P. The inhibition of a diphosphopyridine nucleotidē system by the split products of dimethylaminoazobenzene, *Cancer Research, in press.*

THE HISTORY OF FEVER THERAPY IN THE TREATMENT OF DISEASE*

WILLIAM BIERMAN

Attending Physician in Physical Therapy, The Mount Sinai Hospital

THE idea that fever is a method of therapy may be traced back to the early days of written history. "Give me the power to produce fever, and I will cure all disease," is a quotation attributed to Hippocrates more than twenty-three hundred years ago. Ruphos of Ephesus, four hundred and fifty years afterwards, said: "If indeed any were so good a physician as to be able to produce fever, it would not be necessary to look for any other remedy in sickness."

The production of fever as a therapeutic procedure had to wait centuries, however, for advances in chemistry, physics, mathematics, and medical sciences. The development of fever therapy can be divided into empirical and scientific eras. The borderline between these two eras was thermometry which was introduced in the early part of the Seventeenth Century by Galileo and Sanctorius, and developed in the second half of the Nineteenth Century by Wunderlich and Allbutt.

EMPIRICAL ERA

The origin of therapeutic fever lies buried in medical antiquity. While the rays of the sun have therapeutic value, other than their heating effects, nevertheless, early physicians used them solely for these effects. Heat was also applied to locally affected parts of the body and to its entirety by means of hot water, steam, sand, and mud baths. It is probably true that the ancient therapist might not have been aware of the fact that by these physical means he produced a rise in body temperature. However, our present knowledge of thermotherapy leads us to the reasonable conclusion, based upon the descriptions of the techniques used, that sufficient heating energy was frequently employed to accomplish such an elevation of systemic temperature.

Egyptian physicians during the Fifth Century B. C. applied rules for

* Read May 14, 1941, at the joint meeting of the Section of Historical and Cultural Medicine of The New York Academy of Medicine, and the New York Physical Therapy Society.

sun and heat therapy. In the encyclopedic compilations of Oribasius (325-403 A. D.) of Constantinople, are found quotations from Herodotus, the historian of the Fifth Century B. C., referring to this phase of Egyptian medicine.

Natural hot air caverns connected with volcanic sources were utilized (Oribasius, X, 40). The epic poet Homer (Fifth Century B. C.) clearly established that hot baths for medical purposes were common among the Greeks before the Age of Pericles.

Hippocrates had ideas as to the significance of fever, and modern concepts as to its possibilities. He prescribed hot water and steam baths for "thickened" and "tense" skin, for "spasticity" and for pains of the extremities as well as of the torso. Illustrative is the case history of a man of Athens who was affected with a severe pruritus of his entire body. The skin in all regions was so thickened that he had the appearance of a leper and it was impossible to pinch up the skin anywhere. No one had been able to relieve him. Hippocrates ordered him to go to the Island of Melos where there were hot baths. There he became entirely cured of his itching and the thickening of the skin, but he developed a dropsy and died. This man may have had one of the chronic dermatoses for the treatment of which dermatologists are now finding fever therapy to be of value. It is also possible that this patient may have received burns sufficiently extensive to cause a nephritis which proved fatal.

Among contraindications, Hippocrates mentioned repeated or profuse nasal hemorrhage, which, as an evidence of hypertension, would be included in modern contraindications for fever therapy.

During the reign of Tiberius Caesar, 42 B. C.-37 A. D., Aurelius Cornelius Celsus described the prevailing medical procedures and ideas regarding fever and heat. He wrote of a certain Pretonius who treated persons attacked by fever somewhat as follows: "He had the patient well covered up to excite at the same time a violent heat and thirst. When the fever began to abate somewhat, he made him drink cold water. If he broke out in a violent sweat, the patient was considered cured." "Heat," Celsus wrote, "acts well in eye diseases which are without pain and lachrymation. It is good for all sorts of ulcers but principally those due to cold." The techniques of heat application included wet fomentations, dry packs, steam baths, hot air baths, and sun baths. Celsus claimed that ordinarily heat would "relax the skin and draw forth corrupt humors, and change the condition of the body."

Galen wrote: "It is probable that Erasistratus (an Alexandrian anatomist of the Fourth Century B. C.) was not unaware of the method of treating cases of dropsy by heating in the barrel, a treatment which is highly estimated by other ancient physicians. Indeed, the patients experienced for the entire body an evacuation (sweating) much greater and sooner than in the bath. However, they did not suffer from the heat because they breathed cold air, their heads being outside. If they are deprived of this air, they die quickly." (*Deutil respir.* 4. t. iv.)

Coelius Aurelianus treated wasting, hemoptysis, and dropsy with dry hot air and hot sand baths. A description of the early hot sand bath is found in the works of Oribasius (*Orib.* Col. X, 8). "The summer time is the best because one can then choose the hottest day. Toward morning, there are prepared on the river bank in the deep sand, two or three trenches. These are allowed to become thoroughly heated by the sun. The patient should have digested his last meal and also taken a previous walk or at least had some passive movement. When the air is sufficiently warm and the sand sufficiently heated the patient is laid in the trench and covered with the hot sand as much as he can comfortably bear. The head must be protected from the sun. His face is wiped with a sponge dipped in cold water and if he suffers much he is given something with which to rinse his mouth. If the patient perceives that his body does not heat up at all or that he even becomes chilly because of the sweating he should say so. The attendant will then remove the sand, take him out of the trench, and will place him in the trench alongside in the same way as described above. If necessary, this may be done a third time being guided by the different conditions and according to their strengths."

The American Indians treated fevers with heat. William Penn in a letter to Edward Baynard, a fellow of the Royal College of Physicians, described how an Indian Chief obtained almost immediate relief from an illness associated with fever by the use of hot vapor baths. Among the early Americans, the sweat bath was a favorite therapeutic measure, especially for acute fevers. Arthritis, neuritis, and rheumatism, common among these Indians, were not distinguished from each other, but were all treated alike with the sweat bath. Carolina Indians used hot mud holes for treating various diseases of the extremities. Remittent and other forms of fever prevalent among the inhabitants of Northern Africa, were treated by sweating induced by hot sand and hot water baths.

The Chinese and the Japanese were among the earliest peoples to use their intensely hot springs for therapeutic purposes. In Japan the volcanic formations gave rise to many hot springs. These thermal springs were used for the treatment of all forms of syphilis, arthritis, rheumatism, acute genito-urinary infections, and respiratory, digestive, nervous and ocular diseases. They have been very popular throughout the Japanese empire since the Sixteenth Century and enjoyed local renown for several centuries before that time. Indeed, the use of the thousands of hot springs in Japan was common among all classes of the populace as one of the most important cures long before the introduction of European medicine. At Kusatsu, water gushes out of the bases of ancient volcanoes at a temperature between 100° F. and 160° F. As the water flows into reservoirs, it is unbearably hot, and the bathers stir it with large wooden paddles, thereby cooling it. They then immerse themselves to the neck and pour hot water over their heads with wooden dippers. After three to six minutes of this refined torture, they bob out almost parboiled with a body temperature of between 103° and 105° F.

Scientific Era

The research techniques developed during the Seventeenth, Eighteenth, and Nineteenth Centuries, permitted medical practice to pass from the stage of philosophic argument to scientific reasoning. Galileo in 1595 invented the thermometer, which may be said to have brought science to fever and heat therapy. Galileo's thermometer was the open-air alcohol thermoscope. Shortly afterward, in 1611, Sanctorius introduced this device to clinical medicine. Sanctorius investigated the cause and nature of body temperature. To carry out his studies, he devised the pulsilogium, an instrument for studying the pulse, and applied Galileo's thermoscope. He recognized that the human body has a normal temperature and determined variations from the normal as an aid to diagnosis.

In 1648, Von Helmuth also began to use a clinical thermometer, designed by Leurchon, the Frenchman, who in 1624 gave the name "thermometer" to the instrument.

Ferdinand II, Grand Duke of Tuscany, hermetically sealed the open end of Galileo's thermometer in 1641. Robert Hooke of England, in 1664, proposed that the freezing point of water be taken as one fixed point on the thermometer scale. It is believed that in 1684 he also sug-

gested the boiling point of water as another fixed point.

Fahrenheit described the use of mercury in thermometers in 1714. Herman Boerhaave (1668-1738) of Leyden, the founder of "eclectic" medicine, had been interested in fever and temperature reactions. He directed Fahrenheit to make him some thermometers for clinical use.

In 1742, Celsius of Upsala, an astronomer, proposed "zero" as the boiling point of water and "100" as the temperature of melting ice. The change to modern Centigrade was made independently by two scientists, Christin of Lyons, and Stromer, a colleague of Celsius. Stromer inverted his friend's scale and this revised instrument was used experimentally at Upsala in 1750.

Some of the authors of the Sixteenth and Seventeenth Centuries regarded fever as nature's means of healing. Gomez Pereira and Solenander pointed out the common belief of the Italians that tertiana had a cleansing effect. Primrose quoted the belief of people in England that malaria was beneficial.

An engraving by Jacques Lainet (Paris, 1659) represented the combination of mercury and heat for the treatment of syphilis. Fumigations with mercury were carried out in an oven. The intense sweating along with salivation, was thought to rid the body of disease poisons. "For one pleasure, a thousand pains" was the significant inscription on the oven.

In attempts to discover the exact influence of heat, Boerhaave and his pupil, Prevoost, and Fahrenheit put animals into heated ovens. They found that a dog and a cat died in twenty-eight minutes at a temperature equivalent to 73° C., while a sparrow died in seven minutes.

Influenced by Sydenham's views and by his own observations, Boerhaave finally concluded that fever must not be fought under any circumstances. He wished, he said, that he could produce the febrile curing action by artificial means. "I would be," he said, "the greatest physician if I could produce intermittent fever as easily as suppress it."

John Hunter (1728-1793), the English surgeon, also used the thermometer. Both he and DeHaan opposed the view that the production of heat in the body was due to friction of blood moving in the vessels. George Martine, of Scotland, in 1740 published his clinical-thermometric observations in a paper called "Essays and Observations."

Boerhaave's praise of fever caused a controversy that has persisted up to the present time. Gaub, one of Boerhaave's pupils, believed that

although fever was often salutary, nevertheless, it sometimes was fraught with great danger, especially to the circulation.

In 1790, Metzler made an interesting observation on malarial therapy in a treatise, "On the Advantages of Fever in Long Standing Diseases." This treatise, published in Ulm, was one of the early prophesies of the future therapeutic use of malaria. Metzler wrote: "Vigorot, Broussonet and myself sent patients with congested bowels to such places where they have soon been cured by intermittent salutarious fever."

An important theory on the cause of fever was offered by William Cullen of Edinburgh, in 1777. It was based on the newly acquired facts in the budding field of neuropathology. Virchow one hundred years later was a protagonist of this theory. An elevated temperature of the body, Cullen said, was a paralytic symptom due to depression of a natural influence on heat production. Any disease could become febrile if it extended to the centers of metabolism and suppressed the moderating effect of these centers. Febrile patients were, therefore, subjected to cooling measures by Cullen and his followers.

With rare exceptions, no attempt was made prior to the work of Wunderlich, to obtain more than one or two temperature recordings during an illness. Davy (1788-1829) in mapping out physiologic variations, and Traube (1818-1876), closely following the influence of digitalis on the body's temperature, were among the few who made frequent observations during a twenty-four hour period. The importance of such continued readings escaped them. Traube denied that fever depended upon increased production of heat. Lavoisier's theory of combustion and oxidation had postulated this relationship.

Up to the time of J. Clasius (1850) heat was generally regarded as a material substance. Only after Lord Kelvin (Sir Thomson) in 1849 established his absolute scale of temperature and Clasius and Helmholtz in 1850 worked out the mathematical laws governing heat transformation was the scientific framework for clinical thermometry laid.

In 1868, Carl Wunderlich published his classic on animal heat. Wunderlich demonstrated the diagnostic and prognostic importance of continued temperature observations during the course of a disease. He recorded the temperature of patients every four hours and constructed charts showing its variations. When he stated that fever was a symptom and not a disease, Wunderlich prepared the way for studies on heat production and fever. Wunderlich's method of attaining rectal tempera-

ture curves characteristic of various diseases spread quickly through England and Germany.

The period of the Nineteenth Century that witnessed the introduction of thermometry into clinical medicine was characterized also by advances in knowledge concerning infectious diseases. The record of the temperature of the body became one of the principal means of characterizing various febrile affections and of recognizing complications of these diseases. The close association of infection with fever was soon established and stressed so energetically that at present physicians find it difficult to avoid using one as an indication of the other. Thermometers had begun to make their appearance in numerous English hospitals during 1866-1867, and became generally accepted within the next two years. These were axillary thermometers, large, ten inches long, clumsy, and took five minutes to register. Sir Clifford Allbutt in 1868 reduced their size and devised the clinical mercury thermometer with which we are familiar. Resistance thermometers and thermocouples now permit of the continuous observation and automatic recording of temperature. Thanks to these advances, the thermometer, well-established as the invaluable tool of the diagnostician, has become the compass of the fever therapist.

The practitioners of the ancient and of the medieval world had made therapeutic use of fever produced by physical means on an empiric basis. They did not realize the physiologic significance of the procedure. The voices of those who reacclaimed the value of systemic temperature elevation and stated that fever is a natural mechanism of defense were drowned out under a deluge of antipyretics. Cool packs, showers, and baths, snow and ice were applied with such diligence that at times the doctor in concentrating on his efforts to reduce the fever forgot the patient, and accidents occurred. Less dangerous and simpler antipyretic measures were sought. Sydenham had called attention to the value of quinine in treating the fever of malaria. It came to be generally used for the treatment of other diseases associated with temperature elevation, such as typhus, puerperal infections, and tuberculosis. In these cases quinine proved unsatisfactory. A search for new antipyretics was therefore begun. Salicylic acid, phenol, antipyrin, antifebrin, amidopyrin, followed one another and were prescribed alone, alternately, or together. Chemists, in their laboratory search for antipyretics, discovered many a useful narcotic, analgesic and spasmolytic drug, but the "fever

drug" could not be found.

When Pfluger (1829-1910), as a result of his physiologic studies, ascribed a utilitarian purpose to fever, he was studiously ignored. Welch's supposition, in 1888, that "fever-producing agents light the fire which consumes them" found no response until recent years. Virchow echoed Cullen. Practitioners maintained a continuous attack on temperature elevation in disease. The momentum of these opinions has carried over into our day, so that the alcohol sponge and cold baths still are frequently routine, and the combination of acetylsalicylic acid, phenacetin and caffein has remained a popular method of "reducing the fever."

A clearer and more scientific conception of fever and its beneficial effects was obtained through several revolutionary medical discoveries which resulted in the founding of bacteriology and in an understanding of human metabolism, nutrition, and the physiology of the nervous system. The bacteriologist has shown that, in order to overcome disease, the objective of the clinician should not be the direct suppression of the abnormal elevation of temperature, but rather the destruction of the foreign agents responsible for inflammation and for fever. Further investigations demonstrated that the value of quinine in the treatment of malaria was not due to the influence of this drug upon heat production, heat loss, and heat regulation, but because of its effect upon the plasmodium. The work of men such as Pasteur, Koch, and Behring helped to establish the idea that the body fights for itself, that suffering life helps itself and the art of the doctor should assist the natural power of healing when it is weakened or limited. Modern medicine should no longer concentrate its attention upon the number of degrees of temperature elevation, but upon the profound change in physiologic activity due to this elevation. It should determine to what extent these phenomena are symptoms of the healthy activity of the organism and to what extent they are signs of damage and of loss. We recognize that microörganisms are not the only cause of inflammation and of fever, but that there are a host of thermic, chemical and toxic causes.

As early as 1870 Wunderlich declared that fever is a neuropathologic process. Other outstanding scientists of that time, such as the physiologist Johann von Muller, the surgeon Billroth, and the pathologist, Virchow, agreed that fever is an increase of oxidative processes due to stimulation of the central and peripheral nervous system. Experi-

mental hyperthermia was produced by the famous brain puncture (Warmestich) of Aronsohn and Sachs (1884), who stimulated the corpus striatum, and by Ott (1891), who stimulated the tuber cinereum. The studies of Krehl and his associates further emphasized the neural relationship to fever. The work of Krehl confirms more and more the famous conception of Liebermeister, who had declared that in fever, heat regulation is adjusted to a higher level.

Space does not permit reference to the work of many men who helped develop these fields. These include Lavoisier (1775) who determined the fundamental fact that the quantity of oxygen absorbed and carbon dioxide excreted depends upon food, work, and temperature; Joule, who in 1842 determined the mechanical equivalents of heat; Mayer, Helmholtz, Bischoof, Voit, Rubner, Atwater, Benedict, Lusk, Bazett and many others.

In 1883, W. H. Phillips experimenting upon himself, demonstrated that his temperature could be raised to 103° F. by prolonged immersion in hot water. Fourteen years later, Hill reported the influence of bath temperature upon body temperature and the changes it produced in pulse, blood pressure, and alveolar tension. Others confirmed and added to these findings. These authors included Fox, Sonntag, Weichbrodt and Jahnel, Schamberg, Tseng, Walinski and Mehrtens and Pouppirt.

Kellogg, in 1894, reported that the body temperature, as indicated in the rectum, may rise to 103° F., or even higher, in a prolonged electric light bath. Yet no one thought of using his technique for producing artificial fever for therapeutic effects until 1929, when Kahler and Knollmayer obtained fever temperature by this means.

With the advent of modern electricity, it was soon recognized that one of the effects of an electrical current was thermal. However, no form of electrothermal treatment had been possible until d'Arsonval in 1891 evolved his high frequency current, and showed that it would pass through the human body in a volume as great as three amperes, but without muscular nervous irritation and causing what he called "an unpleasant sensation of heat."

Nikola Tesla, working independently, produced a high frequency circuit and reported his results in the same year as d'Arsonval. He noted the passage of this current through the body and its lack of effects other than heating, which he suggested might be used therapeutically. It remained for von Zeynek, nearly ten years later (1904), working with

von Preyss and von Berndt, to demonstrate the therapeutic application of this current. von Zeynek called the method thermopenetration, while Nagelschmidt finally hit upon the now accepted term *diathermy*.

Notwithstanding the voluminous literature upon diathermy accumulated all over the world, it was not until 1929, nearly forty years after d'Arsonval's discovery, that a sustained fever induced by diathermy was used for therapeutic purposes. Neymann and Osborne, King and Cooke, raised the body temperature by using jacket-shaped electrodes. By means of blankets, they were able to maintain such temperature elevations for several hours.

The recent interest in fever therapy was in a large measure the result of work by Wagner-Jauregg of Vienna and by Whitney of Schenectady. Julius Wagner-Jauregg, after twenty years of observation, began to inoculate paretic soldiers with malaria in 1917. Despite some fatalities and great resistance from his colleagues, his success was so brilliant that ten years later he received the Nobel prize. The beneficial effect of malaria in epilepsy had been known to Hippocrates. Its curative effects in paresis and in insanity had been recorded in more than one hundred and sixty cases before Wagner-Jauregg, according to Maisani. Yet Wagner-Jauregg's work popularized this procedure and established its clinical value so that it received world-wide study.

In order to achieve the same results a host of less noxious proteins than the living malaria plasmodium were tried. Physical agents, such as the hot bath, diathermy, and photothermy were also employed.

In January 1928, Whitney observed that the men working with high-powered short wave tubes employed for long range radio transmission complained of headaches and other discomforts. A physician examining these men before and after work found that exposure to the current developed by these tubes produced two or three degrees of temperature elevation. Although Gosset and his co-workers had treated tumors on geranium plants by means of short waves in 1924, and Schereschewsky had employed currents of very short wave length for the treatment of animal tumors, these workers did not call special attention to the heat-producing effect of these energies. After experimentation on small animals, Whitney placed a number of larger high-frequency oscillators at the disposal of a number of us who were especially interested in the subject. From these and other sources have come new data concerning the physiologic significance of fever and also its thera-

peutic possibilities in the treatment of gonorrhea in all of its manifestations (including cases resistant to the sulfonamides), syphilis of the central nervous system, Sydenham's chorea, rheumatic fever, and in some diseases of the eye and of the skin. A voluminous literature on the subject has been developed consisting of books and articles which have been printed in leading medical journals. At the First International Congress on Fever Therapy held in New York in 1937 much of the data developed in recent years was summarized. There is evidence of the possibility of enhancing the effectiveness of the newer chemical substances by combining their use with purposeful elevations of the body temperature as in syphilis, gonorrhea, and in subacute bacterial endocarditis.

This survey of fever research gives but a bare outline of the painstaking work devoted to this subject in the past years. We tend to view fever therapy as a modern concept because the techniques which we employ to create it are of recent origin. It is therefore of interest to note that this method has been employed by some physicians all through the period of known medical history. Many of the diseases which we treat in this manner today were apparently treated in like fashion during the past centuries. It may well be that we still have something to learn from the ancients, including Petronius who thought that fever should be treated with heat.

In spite of all these efforts of the past, the significance of fever is not sufficiently appreciated today. It is hoped that the precise production of hyperthermia and its control in time and degree by means of the new methods will prove not only a most useful contribution to therapy, but will also start a new chapter in the history of the time-honored problem of fever.

REFERENCES

Allbutt, (Sir) T. Clifford. *Science and mediaeval thought,* London, C. J. Clay & Sons, 1901.

Burton, W. *An account of the life and writings of Herman Boerhaave.* London, H. Lintot, 1746.

Garrison, F. H. *An introduction to the history of medicine.* Philadelphia, Saunders, 4. ed., 1929.

Mitchell, S. Weir. *The early history of instrumental precision in medicine.* New Haven, Little, Morehouse & Taylor, 1892.

Saidman, J. L'oeuvre scientifique d'Arsonval, *Ann. Inst. actin.,* 1933-34, *8:*105.

Wunderlich, C. R. A. *Das Verhalten der Eigenwärme in Krankheiten.* Leipzig, O. Wigand, 1868.

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

American Psychiatric Association. *Biographical directory of fellows and members.*
N. Y., Amer. Psych. Assoc., 1941, 489 p.

Amor, A. J. *An X-ray atlas of silicosis.*
Bristol, Wright, 1941, 206 p.

Belanger, E. J. *Drug and specialty formulas.*
Brooklyn, Chem. Pub. Co., 1941, 307 p.

Bourne, A. W. *Synopsis of obstetrics and gynaecology.* 8. ed.
Bristol, Wright, 1941, 490 p.

Brinton, D. H. *Cerebrospinal fever.*
Edinburgh, Livingstone, 1941, 162 p.

Burgos, H. I. *Contribución al estudio de la alimentación del lactante normal y sano en el primer semestre de vida.*
Buenos Aires, El Ateneo, 1941, 139 p.

Caldwell, J. A. *A manual of the treatment of fractures.*
Springfield, Ill., Thomas, 1941, 150 p.

Crile, G. W. *Intelligence, power and personality.*
N. Y., Whittlesey, [1941], 347 p.

Crossen, H. S. & Crossen, R. J. *Diseases of women.* 9. ed.
St. Louis, Mosby, 1941, 948 p.

Culbertson, J. T. *Immunity against animal parasites.*
N. Y., Columbia Univ. Press, 1941, 274 p.

Davidson, M. *A practical manual of diseases of the chest.* 2. ed.
London, Milford, 1941, 575 p.

Dexter, L. & Weiss, S. *Preeclamptic and eclamptic toxemia of pregnancy.*
Boston, Little, 1941, 415 p.

Eberson, F. *The microbe's challenge.*
Lancaster, Cattell, 1941, 354 p.

Gerard, R .W. *The body functions; physiology.*
N. Y., Wiley, 1941, 289 p.

Goldthwait, J. E.; Brown, L. T.; Swaim, L. T. [et al.]. *Body mechanics in health and disease.* 3. ed.
Phil., Lippincott, [1941], 316 p.

Gray, G. W. *The advancing front of medicine.*
N. Y., Whittlesey, [1941], 425 p.

Hawley, E. E. & Carden, G. *The art and science of nutrition.*
St. Louis, Mosby, 1941, 619 p.

Heidel, W. A. *Hippocratic medicine; its spirit and method.*
N. Y., Columbia Univ. Press, 1941, 149 p.

Hess, J. H. & Lundeen, E. C. *The premature infant.*
Phil., Lippincott, [1941], 309 p.

Huffman, E. K. *Manual for medical records librarians.*
Chic., Physicians' Record Co., 1941, 308 p.

Jessner, L. & Ryan, V. G. *Shock treatment in psychiatry.*
N. Y., Grune, 1941, 149 p.

Johnstone, R. T. *Occupational diseases.*
Phil., Saunders, 1941, 558 p.

Kagan, S. R. *Leaders of medicine.*
Boston, Medico-historical Press, 1941, 176 p.

King, E. S. J. *Surgery of the heart.*
Balt., Williams, 1941, 728 p.

Kracke, R. R. *Diseases of the blood and atlas of hematology.* 2. ed.
Phil., Lippincott, [1941], 692 p.

Lewis, J. T. R. *The principles and practice of diphtheria immunization.*
London, Milford, 1941, 155 p.

Lichtwitz, L. *Functional pathology.*
N. Y., Grune, 1941, 567 p.

Marriott, W. M. *Infant nutrition.* 3. ed.
St. Louis, Mosby, 1941, 475 p.

Martinez Durán, C. *Las ciencias médicas en Guatemala; origen y evolución.*
Guatemala, Sánchez, 1941, 439 p.

McGehee, W. H. O. & Green, M. W. *A textbook of dental pharmacology, materia dentica and pharmaco-therapeutics.* 2. ed.
Phil., Blakiston, [1941], 462 p.

Meakins, J. C. *Symptoms in diagnosis.*
Boston, Little, 1941, 323 p.

Moore, J. E. *The modern treatment of syphi-*

lis. 2. ed.
Springfield, Ill., Thomas, 1941, 674 p.

National Research Council. Committee on Work in Industry. *Fatigue of workers.*
N. Y., Reinhold, 1941, 165 p.

Needham, J. G. *About ourselves; a survey of human nature from the zoological standpoint.*
Lancaster, Cattell, 1941, 276 p.

Oliver, W. W. *The man who lived for tomorrow; a biography of William Hallock Park.*
N. Y., Dutton, 1941, 507 p.

Orr, H. W. *Wounds and fractures.*
Springfield, Ill., Thomas, 1941, 227 p.

Penfield, W. G. & Erickson, T. C. *Epilepsy and cerebral localization.*
Springfield, Ill., Thomas, 1941, 623 p.

Polyak, S. L. *The retina.*
Chic., Univ. of Chic. Press, [1941], 607 p. & 56 leaves.

Posada, R. *El diagnóstico precoz del cáncer.*
San Salvador, Imprenta Nacional, 1941, 147 p.

Ross, T. A. *Lectures on war neuroses.*
London, Arnold, [1941], 116 p.

Sante, L. R. *Manual of roentgenological technique.* [8. ed.]
Ann Arbor, Edwards, 1941, 255 p.

São Paulo (state). Serviço de Profilaxia de Lepra. *O filho do hanseniano am face da infecção leprosa.*
São Paulo, [Revista dos Tribunais], 1941, 136 p.

Steinbrocker, O. *Arthritis in modern practice.*
Phil., Saunders, 1941, 606 p.

Stern, B. J. *Society and medical progress.*
Princeton, Princeton Univ. Press, [1941], 264 p.

Treatment in general practice, edited by H. A. Reimann. 2. ed.
Phil., Davis, 1941, 3 v. & index.

Trotter, W. B. L. *The collected papers.*
London, Milford, 1941, 194 p.

Trotula. *The diseases of women; a translation of Passionibus mulierum curandorum.*
[Los Angeles], Ritchie, 1940, 52 p.

Université de Lausanne. *Cinquantenaire de la Faculté de médecine de Lausanne, 1890-1940.*
Lausanne, Roth, [1940], 171 p.

White, J. C. & Smithwick, R. H. *The autonomic nervous system.* 2. ed.
N. Y., Macmillan, 1941, 469 p.

Winter, L. *Operative oral surgery.*
St. Louis, Mosby, 1941, 877 p.

Youmans, J. B. *Nutritional deficiencies.*
Phil., Lippincott, [1941], 385 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

NOVEMBER 6—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Amendment to By-Laws; c] Report of Nominating Committee. ¶ Papers of the evening. Aviation Medicine—a] The relation of the medical and physical sciences in the development of aviation, Detley W. Bronk, Ph.D., Sc.D., Professor of Biophysics and Director of the Johnson Research Foundation, University of Pennsylvania School of Medicine; b] The use of oxygen in aviation medicine, John R. Poppen, Captain, Medical Corps, U.S.N., Bureau of Aeronautics, Washington; c] Bends and the effects of acceleration, John F. Fulton, Sterling Professor of Physiology, Yale University School of Medicine. ¶ Report on election of Fellows.

NOVEMBER 27—*The Harvey Society in affiliation with The New York Academy of Medicine.* The second Harvey lecture, "Factors Conditioning Resistance to Epidemic Influenza," Thomas Francis, Jr., Professor of Epidemiology, School of Public Health, University of Michigan.

SECTION MEETINGS

NOVEMBER 5—*Dermatology and Syphilology.* Presentation of cases—The Mount Sinai Hospital. ¶ General discussion. ¶ Executive session.

NOVEMBER 7—*Surgery.* Reading of the minutes. ¶ Presentation of cases—a]1. A case of congenital overgrowth of a finger to huge proportions, with postoperative result, 2. A case of mucocele of the appendix with pseudomyxoma of the peritoneum, Francis X. Timoney; b] A case of primary pneumococcus peritonitis in an adult treated by exploration, sulfathiazole and specific serum, with recovery, Robert A. Wise. ¶ Papers of the evening—a] Thoracoscopy and pneumonolysis. Observations on 100 consecutive cases, Louis Carp, Borris A. Kornblith; b] Surgical problems of the present war, Fraser G. Gurd, McGill University (by invitation). ¶ General discussion. ¶ Executive session.

NOVEMBER 11—*Combined Meeting of the Section of Neurology and Psychiatry and the New York Neurological Society.* Reading of the minutes. ¶ Case presentation—Choreo-athetosis and athetosis, a clinico-pathological report, M. Neustaedter; Discussion, Tracy J. Putnam. ¶ Papers of the evening—a] Mimetic smiledness as related to handedness: an indicator of basic modes of human adaptation, John G. Lynn (by invitation); Discussion, Charles Davison; b] Marginal dyskinesias and dyssynergias as diagnostic adjuncts (Moving pictures), Byron Stookey, Lester Mount (by invitation); Discussion, Israel S. Wechsler.

NOVEMBER 12—*Combined Meeting of the Section of Historical and Cultural Medicine and the New York Society for Medical History.* Reading of the minutes. ¶ A symposium on approaches to medical history, Richard Harrison Shryock (by invitation), Iago Galdston, George Rosen (by invitation), Fritz Wittels. ¶ General discussion.

NOVEMBER 12—*Pediatrics.* Round table discussion—School Health Regulations, Philip M. Stimson, Chairman. From the view point—a] Of the public school, Isidore H. Goldberger; b] Of the private school principal, Millicent C. McIntosh (by invitation); c] Of the private school physician, Katherine Dodge; d] Of the parents, Virginia Fox Patterson (by invitation); e] Of the Bureau of Preventable Diseases, Department of

Health, Samuel Frant (by invitation); f] Of the Department of Health, Haven Emerson. ¶ Executive session.

NOVEMBER 17—*Ophthalmology.* Executive session—Reading of the minutes. ¶ In memoriam—Francis Wayles Shine, Bernard Samuels. ¶ Presentation of cases—a] Tuberous sclerosis in a five-months-old infant, Isadore Givner; Discussion, F. L. P. Koch (by invitation); b] Actinomycosis of the conjunctiva, associated with superficial punctate keratitis, Gordon Bruce; Discussion, James K. Duryea; c] Lymphosarcoma of the lacrimal gland, Charles A. Perera; Discussion, Maynard C. Wheeler. ¶ Papers of the evening—a] Vollmer Patch Test; its possibilities in ophthalmic practice, Benjamin Friedman and Frank Keil, Jr. (by invitation); b] Current studies on the mechanism of formation of the intraocular fluids, Jonas S. Friedenwald, Baltimore (by invitation); Discussion to be opened by Ludwig V. Sallmann (by invitation).

NOVEMBER 18—*Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Bone marrow—diagnostic and therapeutic considerations, Maurice Morrison (by invitation); b] Treatment of leukemia by radioactive phosphorus, Lloyd F. Craver; c] Hematologic complications following chemotherapy, Nathan Rosenthal; d] The differential diagnosis of the hemolytic anemias, Thomas Hale Ham, Thorndike Memorial Laboratory (by invitation); Discussion, William Dock (by invitation), Paul Reznikoff. ¶ Executive session.

NOVEMBER 18 — *Genito-Urinary Surgery.* Reading of the minutes. ¶ Papers of the evening—a] Manipulative treatment of ureteral calculi, William Niles Wishard, Jr., Indianapolis (by invitation); b] Carcinoma of the ureter—report of five cases, Albert Bothe, Philadelphia (by invitation); c] Modification of the Higgins technique of uretero-intestinal anastomosis, Joseph A. Hyams; Discussion, Benjamin S. Barringer, Henry G. Bugbee, Thomas J. Kirwin. ¶ General discussion. ¶ Executive session.

NOVEMBER 19—*Otolaryngology.* Executive session—Reading of the minutes. ¶ Papers of the evening—a] Effect of tonsillectomy on respiratory infections in children, Albert D. Kaiser, Rochester, New York (by invitation); b] Relationship of tonsil and sinus infections to chronic arthritis, Ralph H. Boots; c] Effect of tonsillectomy on nephritis, John Lyttle; Discussion, Westley M. Hunt, Robert L. McCollom (by invitation). ¶ General discussion.

NOVEMBER 21—*Orthopedic Surgery in conjunction with the Philadelphia Orthopaedic Club.* Reading of the minutes. ¶ Papers of the afternoon (*Discussion by invited speakers*)—a] Congenital absence of tibia, lower half, bilateral, aged 15 years. Result of observation and treatment since early infancy, Arthur Krida; Discussion, J. T. Rugh; b] Femoral ischial transplant, David M. Bosworth; Discussion, Bruce Gill; c] Angioma of tarsal bones, Samuel Kleinberg; Discussion, George Wagoner; d] Suspensory ligament operation for pathological dislocation of the hip following poliomyelitis, Joseph B. L'Episcopo; Discussion, B. F. Buzby; e] Eosinophilic granuloma of bone, Henry L. Jaffe; Discussion, Irvin Stein; f] The laminagraph as an aid in the treatment of chronic oseomyelitis, Alan DeForest Smith and Lawson E. Miller; g] Observations in the topical use of sulfone derivatives, Major Edgar M. Bick; Discussion, A. R. Shands, Jr.; h] A case of Guillan-Barré disease, H. Leslie Wenger; Discussion, A. M. Rechtman; i] Stenosing tenovaginitis of the thumb in infants, Isidore Zadek; Discussion, Rutherford L. John; j] Arthroplasty of the first metacarpal greater multangular joint for dysfunction following a malunited Bennett's fracture, Nicholas S. Ransohoff; Discussion, Ernest Brav; k] A modified operation for opponens

paralysis, T. Campbell Thompson; Discussion, J. T. Nicholson. ¶ Executive session—Special election, John C. McCauley, Jr., for Secretary.

NOVEMBER 25—*Obstetrics and Gynecology. (Program presented by the Obstetrical Department of the Morrisania Hospital.)* Executive session—Reading of the minutes. ¶ Presentation of cases—a] Macrocytic anemia of pregnancy, Mark Daniel (by invitation); Discussion, Bernard S. Kahn (by invitation); b] Unilateral cortical abscesses of kidney, complicating pregnancy, Frederick A. Wurzbach, Jr.; Discussion, Thomas M. Mulcahy (by invitation); c] Blood transfusion reaction due to atypical agglutinins, Philip Crooks (by invitation); Discussion, A. S. Weiner (by invitation) and Philip Levine. ¶ Papers of the evening—a] Management of unengaged vertex presentations in primiparae, Abraham B. Tamis and Jacob Clahr; Discussion, Milton J. Goodfriend; b] Contractions of the human uterus in pregnancy and labor, Leo Wilson. ¶ General discussion.

AFFILIATED SOCIETIES

OCTOBER 30—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Paper of the evening—The pathology of diabetes mellitus, Shields Warren, Boston (by invitation): Discussion by Arthur C. Allen (by invitation, Irving Graef. ¶ Executive session.

New York Roentgen Society—Because of conflict in dates with the Graduate Fortnight, this Society held no meeting in October.

NOVEMBER 17—*New York Roentgen Society in affiliation with The New York Academy of Medicine.* Papers of the evening—a] The roentgen features of carcinoma of the lung in relation to operability, I. Sarot (by invitation); b] The preoperative localization of lung abscess, C. B. Rabin (by invitation); c] Sectional radiography in the recognition of suppurative lung disease, Marcy L. Sussman. ¶ Discussion, H. Neuhof (by invitation), H. Wessler (by invitation). ¶ Executive session.

NOVEMBER 27—*New York Pathological Society in affiliation with The New York Academy of Medicine.* Presentation of cases—a] Uterine tumor of endometrial stroma type, Amour F. Liber, Chester R. Brown; b] Myoblastoma of voluntary muscle with lipid-containing cells, Chester R. Brown, Amour F. Liber. ¶ Papers of the evening—a] Infection with organisms of the Salmonella group, Siegbert Bornstein (by invitation); b] Lymphosarcoma with special reference to the original site, Nicholas M. Alter. ¶ Executive session.